Atrophic Rhinitis

From the Voluptuary Nasal Pathology to the Empty Nose Syndrome

Stefano Di Girolamo
Editor

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Foreword

It is with pleasure that I have accepted to present this book edited by Professor Stefano Di Girolamo, a pleasure resulting from the affection, esteem, and respect that have bound me to him for over 20 years.

In fact, many years ago I could recognize several uncommon qualities in that young medical doctor, who was preparing to start the training course at the School of Specialization in ENT Clinic at the University of Siena, directed by me.

Over the years he has shown himself to be a good clinician, an acute researcher, and a clever surgeon.

Once he obtained the qualification with the highest marks, our paths were divided; however, I had the opportunity to follow the development of his skills in different universities.

Now he holds the most prestigious position that an academic can achieve in his own specialty: he directs, as full professor, the ENT Clinic of the University of Rome "Tor Vergata" with those excellent qualities I had the opportunity to detect in Siena, and this can only please me and give me a certain satisfaction.

Returning to the book, atrophic rhinitis is undoubtedly a pathology that occurs quite often, and the extent of which is difficult to be defined along with the establishment of an effective treatment.

The different forms and symptoms, together with the multiple clinical pictures, are the reason for these difficulties.

With this book, the authors want to examine in depth most of the topics related to this interesting pathology and even more to suggest some treatments.

To achieve this goal, the book includes chapters that fully characterize all the related aspects.

In fact, pathophysiological, clinical, and surgical aspects are taken into consideration, presented, and discussed, analyzing all the issues related to this pathology: from the role of different investigations, to the various medical and surgical therapies, through the clinical evaluation with subjective questionnaires and psychological evaluation.

Undoubtedly, the reading of the chapters will be useful to health workers, but it will help even more to encourage the study of the topic and will stimulate new researches towards a definite knowledge of it.

Regarding the empty nose syndrome (ENS), this term encloses many pathological forms that are characterized by different anatomy and different symptomatologic pictures.

From a pathophysiological point of view, ENS follows on from functional interventions on the nasal cavities sometimes performed in an excessively demolitive way.

Moreover, ENS could be also included in the umbrella definition of Secondary Atrophic Rhinitis.

For a correct nasal physiology, especially in the functions of heating and humidification, the lower, middle, and upper turbinates are fundamental elements whose conservation must always be considered indispensable.

When the nasal physiology, especially in the ventilatory function, is disturbed by an irreversible hypertrophy of the turbinates, it is necessary to proceed with a surgical intervention that must always be as much conservative as possible, among the dozens of methods proposed in the literature, at least preserving the mucosa.

Anyway empty nose syndrome remains highly controversial, with aggressive inferior turbinate reduction or mucociliary dysfunction frequently implicated.

Since anatomical and clinical pictures can be very different, in order to speak a common and scientifically useful language for comparisons and statistics, it would be really appropriate to have a classification of this syndrome that can differentiate, at least at a general level, the postsurgical situations often related to different symptomatologic pictures.

I wish you all a pleasant and fruitful reading.

Desiderio Passali
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Introduction

Truth is as you see it. As I see it, for clarity and to reduce confusion, atrophic rhinitis should specifically be classified and subdivided into:

1. Primary atrophic rhinitis.
2. Secondary atrophic rhinitis.

Previous terminologies found in the literature for atrophic rhinitis added to the confusion by using the terms atrophic rhinitis, rhinitis sicca, and ozena interchangeably, at times utterly without the precise definition or differentiation. Most assuredly, atrophic rhinitis is a debilitating nasal mucosal progressive disorder with a constellation of conspicuously prominent "hallmark" symptoms including:

1. nasal dryness and crusting,
2. foul (fetid) odor,
3. epistaxis,
4. nasal airway obstruction,
5. facial pain,
6. headache,
7. anosmia,
8. psychological depression.

What is almost universal and remarkable is the wide-open intranasal airway, yet the patient often paradoxically complains of the symptom of nasal airway obstruction (difficulty breathing despite the broadly patent nasal airway).

The principal purpose of this book is a contemporaneous examination of atrophic rhinitis, attempting to eliminate confusion in terminology by presenting the subject with objective clarity and a definitive classification into *Primary* and *Secondary* Atrophic Rhinitis.

To achieve these goals the invited authors are investigating numerous significant subjects encompassing the following topics: primary, secondary, and iatrogenic atrophic rhinitis, the "empty nose" syndrome (ENS), underlying issues of etiology, symptomatology, contemporary diagnostic modalities including use of questionnaires, cytology, computational fluid dynamics readings, nasal airflow analyses besides studying the utility of imaging studies (CT scan, Cone Beam, and MRI).

Matters of treatment algorithms for medical and surgical intervention including mucosal flaps, submucosal injections (augmentations), nasal septal repair, autografts including conchal cartilage, costal (rib) cartilage, bone (hip and calvarial) and use of allograft donor tissues, and other biologicals and inorganic materials are expansively explored.

Primary atrophic rhinitis, often called ozena, is merely the descriptive Greek term meaning "stench" (strong unpleasant odor) and has decreased in incidence in the Western world, during the past 100 years, which is likely due to the liberal use of antimicrobials for chronic nasal infections. While the exact etiology of *primary* atrophic rhinitis is unknown what is known is that almost all of these *primary* atrophic patients have culture-positive bacterial infections with *Klebsiella ozaenae.* On the other hand, patients with *secondary* atrophic rhinitis rarely demonstrate positive cultures for *Klebsiella ozaenae.*

In essence, *primary* atrophic rhinitis is of unspecified etiology, with a spontaneous onset, and a slowly progressive course, while *secondary* atrophic rhinitis, by definition, develops subsequent to either surgical or nonsurgical nasal trauma or may follow a nasal manifestation of a specific systemic disease.

Secondary atrophic rhinitis patients consistently have a number of predisposing factors for developing the "hallmark" symptom complex of atrophic rhinitis.

First let us consider the notorious surgical procedures on the nasal turbinates, especially on the inferior turbinate, but certainly may include procedures or excision of the middle turbinate. Any one of the schemes for reducing the turbinate volume, to alleviate nasal breathing obstruction, may induce the "empty nose" syndrome (ENS), yielding and producing a *secondary* atrophic rhinitis, which may not occur instantaneously but only materialize years following the initial surgical trauma. I deliberately chose the term scheme since there is a monumental list of procedures designed to treat hypertrophy of the inferior turbinate including but not limited to the following catalog as described by Passali D. (1999) and by Huizing H.(2000): electrocautery, chemocoagulation, lateralization by out-fracture, submucosal resection of the conchal bone, cryosurgery, laser surgery, radiofrequency radiation, submucosal resection (with or without powered instrumentation such as shavers), submucosal corticosteroid injection, submucosal sclerosing agent injection, partial turbinectomy plus the infamous total turbinectomy. In all likelihood, this is a somewhat partial and incomplete list documenting the historical attacks on any of the turbinates but principally the inferior turbinate, almost always minus any preoperative functional physiological testing.

There are a number of systemic ailments that the rhinologist needs to be interested in, such as a lymphoma with epistaxis or midline destructive lesions having various names such as idiopathic midline granuloma or lethal midline granuloma or polymorphic reticulosis, because these systemic maladies may have a rhinologic presentation. Granulomatous disorders including sarcoidosis or mycobacterial tuberculosis or other rarer infectious diseases may present with nasal obstruction, crusting, epistaxis, anosmia, and face pain. Autoimmune diseases such as granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) may present with mucosal crusting, nasal obstruction, foul (fetid) odor, and epistaxis.

Relapsing polychondritis is an autoimmune disorder that has the nasal manifestations of crusting and epistaxis. Relapsing polychondritis may coexist with an underlying malignant disease. Churg-Strauss syndrome is a small to medium sized vessel granulomatous necrotizing vasculitis that can present with crusting and epistaxis.

Sjogren's syndrome is a progressive autoimmune inflammation with nasal manifestations of nasal obstruction, dryness, crusting, epistaxis, and hyposmia.

These disorders must be considered in the differential diagnosis of nasal atrophic changes that require: general bacterial culture and sensitivity, analysis for acid-fast bacillus, fungi, and anaerobes. In addition, intranasal tissue biopsy is required along with routine blood studies in addition to investigations of the sedimentation rate, C-reactive protein, antineutrophil cytoplasm antibodies (c-ANCA), and other serologic assays as indicated. Consultation with colleagues in internal medicine, infectious disease, and rheumatology is often required.

While *secondary* atrophic rhinitis, in this classification, is much more frequently encountered than *primary* atrophic rhinitis, both share the same symptoms with the differentiating observation that each possesses completely different etiologies.

In summary, the clinician may distinguish between *primary* and *secondary* forms of atrophic rhinitis as follows: *primary* atrophic rhinitis is defined when the "hallmark" symptoms occur without a definite antecedent cause or trigger in the absence of surgical or nonsurgical nasal trauma, without any evidence of granulomatous or inflammatory autoimmune diseases, and a culture positive for *Klebsiella ozaenae,* while *secondary* atrophic rhinitis has a definitive and indisputable antecedent cause and a bacterial culture finding almost always negative for *Klebsiella ozaenae.*

Overall, atrophic rhinitis is a debilitating chronic disorder heralded by a constellation of symptoms, first of all the common complaint of nasal airway obrstuction despite an abnormally patent nasal passage. Diagnosis is made by history, physical examination, classic symptomatology confirmed with imaging studies, biopsy with histology, while considering a differential diagnosis and ruling out systemic illness. It must also be acknowledged that changes in the nasal mucosa are an inevitable part of the aging process. With an ever-increasing elderly population, newly descriptive terms have been introduced into the literature such as "geriatric" rhinitis, "senile" rhinitis, or the rhinitis of "aging," all of which describe the atrophic nasal mucosal changes secondary to a loss of submucosal serous and goblet cells, decrease of collagen, and an alteration in mucosal microvascular blood flow. Certainly, the rhinitis of "aging" is an example of *secondary* atrophic rhinitis. Senior citizens often have thin atrophic nasal mucosa and symptoms of nasal crusting, thickened nasal secretions, nasal obstruction, and a decrease in olfactory acuity. Complicating issues include the fact that many older patients are medicated with diuretics, beta blockers, and psychological medications that have known side effects including nasal dryness and difficulty breathing, secondary to nasal airway obstruction.

Medical management can be extremely effective with the realistic goal of controlling symptoms. Using topical aminoglycoside irrigations along with intermittent and prudent use of systemic antibiotics based upon culture and sensitivity studies can be very effective in relieving a patient's discomfort. Topical irrigations with tetracycline, aminoglycosides, and more recently ciprofloxacin have been reported

to be both useful and successful. It is usually best to avoid topical steroids and/or topical vasoconstrictor agents since many of these patients regularly suffer from a compromised vascular and/or immune system.

Surgical therapy can be extremely beneficial in the post-traumatic, postsurgical *secondary* atrophic rhinitis as seen in the "empty nose" syndrome patient. As more knowledge is gained regarding the ideal implant material and the exact locus of placement of these materials in correctly selected patients, many may benefit mightily from surgical intervention. Short-term results have been encouraging with the various materials to restore intranasal volume; however, definitive outcomes can only be accurately assessed years after surgical intervention. In other words, only long-term results, with years of postsurgical follow-up, should be pondered before declaring definitive statements.

Certainly, the old adage "an ounce of prevention is worth a pound of cure" pertains to therapeutic surgical manipulation (treatments) of the nasal turbinates. As surgeons, we fully recognize there remains much to understand about nasal physiology so any surgical intervention avoids the untoward result of *secondary* atrophic rhinitis. In addition to therapeutic benefit, prevention of *secondary* atrophic rhinitis is a crucial part of nasal surgery especially since the exact and indispensable amount of nasal mucosa to be preserved during intranasal surgery is still unknown; therefore, be a minimalist in the operating room especially when operating on the inferior and or the middle turbinate, as minimal intervention and maximum preservation should be the words of the day, of the week, of the month, and likely for years into the future.

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Part I

Primary Atrophic Rhinitis

Primary Atrophic Rhinitis: Ozaena and Other Infective Forms

1

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Primary atrophic rhinitis is a progressive chronic nasal disease characterized by sclerotic transformation of the mucous membrane and increased patency of the nasal passages due to atrophic changes in the underlying bones and mucosa [1, 2]. Histopathologically, the ciliary columnar epithelium which lines the nasal cavity is maximally lost and there is squamous metaplasia along with chronic inflammatory changes involving infiltration of monocytes, macrophages, and fibroblasts. Two different types of vascular involvement occur in PAR [3]. Type 1, which is more common, involves endarteritis obliterans, whereas type 2 is associated with capillary vasodilatation.

Primary atrophic rhinitis is a common condition in tropical countries like India, Pakistan, and Bangladesh. The condition usually affects young- and middle-aged adults, especially females (F:M = 5.6:1) [4].

1.1 Etiology of Primary Atrophic Rhinitis

Etiology of primary atrophic rhinitis is still a debatable topic, and it has kept various stakeholders like otorhinolaryngologists, microbiologists, epidemiologists, etc., interested for more than 100 years. Factors involved in its genesis include

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autoimmunity, chronic sinus infection, hormonal imbalance, poor nutritional status, heredity, and iron deficiency anemia [5]. Chronic bacterial infection is considered one of the major causes of primary atrophic rhinitis, especially in highly densely populated regions of the world like countries of Southeast Asia, because sinonasal bacterial infections are contagious.

1.1.1 Bacteriology

Klebsiella Ozaenae is considered the most common causative agent [5]. Other infectious agents which have been implicated include *Coccobacillus foetidus-ozaenae*, *Bacillus mucosus*, *Diphtheroids bacillus*, *Bacillus pertussis*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Proteus mirabilis,* and *Staphylococcus aureus* [4]. According to the experience of physicians who treat upper respiratory tract infection, one cannot be sure whether these bacteria cause the disease or are merely secondary invaders. Few researchers have also isolated *Escherichia coli* from cases with primary atrophic rhinitis [6, 7]. Nutritional deficiency especially iron, fat-soluble vitamins like A, D, E, and K, and proteins leads to an increased susceptibility to recurrent upper airway infections [5].

1.1.2 Virology

With our experience during COVID-19 pandemic, various reports of development of loss of smell or anosmia in patients suffering from coronavirus infection have come to notice. It has to be investigated in detail that viruses causing flu-like symptoms like *rhinovirus*, *parainfluenza virus*, *respiratory syncytial virus*, *adenovirus*, *influenza virus,* and *coronavirus* could be the initiating agent which eventually leads to superimposed bacterial infection. There are many mechanisms that could be attributed for this. Viruses can damage ciliated cells, resulting in ciliostasis and therefore deterioration of mucociliary clearance [8]. Viruses also increase the risk of bacterial adherence to sinonasal mucosa, for example, rhinoviruses upregulate the expression of PAFR (platelet-activating factor receptor). One more example is TLR4 and TLR5 (toll-like receptors) pathways are altered after influenza virus infection resulting in decreased neutrophil attraction, thereby leading to increased bacterial attachment to the airway epithelial cells [9]. Literature is limited in establishing direct link between role of viral infections in atrophic rhinitis hence needs more multicenter studies to be confirmed.

1.1.3 Mycology

Concomitant fungal infection like *aspergillus* species have been isolated from patients diagnosed with atrophic rhinitis. Though no multicenter studies confirm the role of fungal infections in atrophic rhinitis, our clinical experience suggests that it is mainly due to contamination or nosocomially acquired. The only patients where

we saw *aspergillus* species as primary agents were cases of invasive fungal sinusitis causing atrophy.

All patients with a suspect of atrophic rhinitis should be subjected to detailed history, clinical examination including diagnostic nasal endoscopy, radiological examination, and laboratorial testing. In our practice, we do nasal swabbing at three consecutive intervals, 3–5 days apart and confirming the causative agent. The fourth and fifth nasal swabbing are done 1 month after confirmation and initiation of treatment and 6 months after completion of treatment, respectively.

1.2 Clinical Presentation

1.2.1 Signs

There are no reliable objective physical exam findings for the diagnosis of PAR. On endoscopic exam, patients universally have thick, adherent crusts that are yellow-green to gray-black. On removal of the crusts, marked atrophy of the turbinates, especially the inferior ones, can be seen. The turbinate atrophy creates an excessively patent nasal passage through which the posterior nasopharynx and upper portions of the soft palate can be seen. The nasal mucosa is markedly thin, pale, shiny, and bleeds easily. Less frequently encountered clinical signs of atrophic rhinitis include septal perforation, columellar necrosis, and a depressed nasal bridge [10].

1.2.2 Symptoms

Patients typically complain of excessive nasal crusting and "paradoxical" nasal obstruction despite the fact that the nasal cavities are actually enlarged, and foul smell emanating from the nasal cavity that is a source of embarrassment and occasional social rejection [11]. The sense of obstruction may be the result of crusting or disrupted airflow [12]. Other associated symptoms include facial pain, headache, mucosal dryness, dyspnea, epistaxis, sleep disturbance, and occasional mucopurulent rhinorrhea and anosmia. This last symptom most likely occurs as a result of atrophy of the olfactory epithelium in the nasal roof [13]. The feeling of "not getting air" is not alleviated with mouth breathing and often has a negative impact on psychological wellbeing, which manifests as anxiety, depression, anger, frustration, irritability, and fatigue. A unique symptom is *aprosexia nasalis*, where the patient becomes extremely preoccupied with the attempt to maintain a sensation of breathing such that they experience chronically decreased concentration [14].

1.3 Histopathology

Histopathologic studies demonstrate atrophic rhinitis to be a chronic progressive inflammatory process associated with atrophy and fibrosis. It is limited to the nasal mucosa, as the respiratory epithelium undergoes metaplastic change from ciliated

pseudostratified columnar to squamous epithelium with four distinct layers. The flattened squamous epithelium loses its ability for mucociliary clearance leading to secondary crusting. In addition, glandular atrophy occurs, affecting both serous and mucous elements. The remaining seromucinous glands fail to function properly, leading to decreased moisture availability and further crusting. Scanning electron microscopy shows that cilia are scarce or absent and that the mucus droplets that are produced appear to repel each other, making the mucus blanket ineffective. Universal findings include loss of cilia, goblet cells, and compound alveolar glands. Vascular structures are also affected in the disease process. Characteristic changes include endarteritis obliterans with associated thickening of the media and dilatation of the subepithelial capillaries [3]. Combined, these processes lead to poor circulation and decreased moisture and additional crusting. The damage to the cilia and mucosa found in atrophic rhinitis may contribute to the concurrent high incidence of sinusitis.

1.4 Diagnosis

Primary atrophic rhinitis is largely a diagnosis of exclusion focused on evaluation for the causes of secondary atrophic rhinitis. Long bereft of uniformly accepted diagnostic criteria, Ly et al. have offered seven signs and symptoms associated with 95% sensitivity and 77% specificity in their study of 22 patients. Each of the criteria must have been present for at least 6 months and include patient report of chronic nasal obstruction, recurrent epistaxis, and episodic anosmia or documentation by a physician of nasal purulence, nasal crusting, and two or more sinus surgeries. A final element, which more clearly identifies secondary atrophic rhinitis, is the identification of a chronic inflammatory disease associated with granuloma formation [15].

The diagnosis of atrophic rhinitis is made clinically and confirmed by carefully obtained endoscopically guided middle meatal cultures. Nasal biopsy specimens can show loss of the normal pseudostratified columnar epithelium and atrophy of the mucus glands. A nasal culture identifying *K. ozaenae* strongly suggests the diagnosis and the isolation of other associated organisms is also helpful. Multiple microorganisms are frequently cultured, including *Proteus*, *Escherichia coli*, *Staphylococcus aureus*, *pneumococci*, *Perez–Hofer bacillus*, and an atoxic form of *Corynebacterium diphtheriae*. *K. ozaenae* is an encapsulated gram-negative rod that is most often associated with and isolated in this disease. *K. ozaenae* displays a ciliostatic effect by creating intraciliary adherence that leads to poor mucociliary clearance.

The use of the endoscope is critical to obtain culture material and to avoid contaminated cultures. Characteristic nasal features include enlarged nasal cavities, resorption of the turbinates, mucosal atrophy, thick crusts, and ozena. The foul odor of atrophic rhinitis appears to be the most distressing symptom.

Because of the high incidence of concurrent sinusitis, CT is frequently included in the diagnostic evaluation of atrophic rhinitis. Pace-Balzan et al. list characteristic

changes identified by CT as the following: (1) Mucosal thickening of the paranasal sinuses. (2) Loss of definition of the osteomeatal complex secondary to resorption of the ethmoid bulla and uncinate process. (3) Hypoplasia of the maxillary sinuses. (4) Enlargement of the nasal cavities with erosion and bowing of the lateral nasal wall. (5) Bony resorption and mucosal atrophy of the inferior and middle turbinates. The expansion of the nasal cavities at the expense of the maxillary sinuses is the most prominent CT feature. An additional finding is the decreased extent of anteroposterior pneumatization of the maxillary sinuses [16, 17].

1.5 Management

1.5.1 Medical Therapy

The goal of therapy is to clear secondary bacterial infections, reduce the amount of crusting, and relieve the associated foul odor. Routine mechanical crust removal under rigid endoscopic guidance is an important part of therapy. At home, the patient must practice vigorous intranasal cleansing with a salt water or sodium bicarbonate solution. As methanol appears to directly activate cool thermoreceptors within the nasal mucosa, it may be added to nasal lubricants. Use of a cool mist humidifier at home may be beneficial. For those with severely debilitating symptoms and psychological manifestations, referral to psychosocial services is appropriate.

Since the vascular supply is already compromised, vasoconstrictive nose drops should be avoided. Long-term antibiotic use, guided by sinus cultures and sensitivities, is the mainstay of medical therapy. Although tetracycline has traditionally been used to treat this disease, more recent studies suggest the use of ciprofloxacin. Borgstein et al. report success with a regimen of ciprofloxacin 250 to 500 mg twice a day for 4 weeks [18]. Dudley suggests direct instillation of a topical aminoglycoside into the nose to avoid systemic absorption and to increase the availability to the nasal mucosa [19]. However, purulent secretions, which appear to be the best indicator of active disease, may interfere with aminoglycoside efficacy because their activity decreases as the pH level decreases. Superimposed acute bacterial sinusitis is a clear indication for the appropriate systemic antibiotics.

As Mitomycin-C has antiproliferative effects through its ability to inhibit fibroblast activity, the drug has been used as an antiscarring treatment after various ophthalmologic procedures since 1980. Using Mitomycin-C after endoscopic sinus surgery can reduce postoperative adhesions. The new use of Mitomycin-C in PAR has significantly reduced the degree of scabbing and the severity of epistaxis, and it has enhanced the normalization of secretion. Therefore, the topical use of Mitomycin-C associated with continued medical treatment is recommended in patients with a PAR [20].

Occasionally, medical management does not yield satisfactory results, and surgical intervention is required.

1.5.2 Surgical Therapy

A variety of surgical procedures to treat primary atrophic rhinitis exists. Each operation attempts to close or narrow the nasal cavity and to make the air passage more physiologic. The primary goal of surgical therapy is the reduction of symptoms to improve quality of life. Young's operation describes bilateral closure of the nostrils one side at a time at a 3-month interval. This procedure can be performed at any age and, by report, is surprisingly well tolerated. Modification of Young's procedure is described by Gadre et al. Partial nostril closure reduces the nares to a diameter of 3 mm or less. The advantage yielded by partial closure is that it allows for serial endoscopic examination [21]. Rigid nasal endoscopy demonstrates a significant decrease in the amount of crusting present by 1 month after surgery, with almost complete disappearance of crusts by 6 months. In addition, by scanning electron microscopy, cilia tend to increase in length and appearance but not in number after closure. The length of closure varies from 3 to 5 years depending on whether one or both nostrils are involved. The surgical slit provided in a modified Young's operation allows endoscopy to show the most appropriate time to reverse the closure. Implantation of various materials to decrease the nasal lumen patency has also been used to manage atrophic rhinitis. However, artificial implants of acrylic resin and Dacron are extruded in up to 80% of cases. Earlier, Girgis described the use of a dermofat graft placed in the nasal floor through a sublabial incision [5]. Autogenous bone graft material harvested from the iliac crest and implanted in the nasal septum, floor, and lateral nasal wall is referred to as endonasal microplasty. As with the dermofat graft, the major problem encountered with bone graft is the tendency for reabsorption. Finally, Rasmy describes an osteoperiosteal flap with bone from the anterior wall of the maxillary sinus to form the obturating membrane for nasal closure [22].

Treatments may ameliorate but will not cure atrophic rhinitis. Allergists should seek to become familiar with atrophic rhinitis because of the overlap of symptoms with other forms of chronic rhinosinusitis as well as the common presence of concomitant allergic rhinitis in these patients. The progressive nature, poorly understood etiologic mechanisms, and several contributing or concurrent disease processes related to primary atrophic rhinitis render a multidisciplinary approach to management essential.

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Part II

Secondary Atrophic Rhinitis

Secondary Atrophic Rhinitis: Autoimmune and Granulomatous Forms

2

Laura Gigante, Andrea Zoli, Pier Giorgio Giacomini, and Angelo Zoli

Atrophic rhinitis is characterized by progressive nasal mucosal atrophy, nasal crusting, fetor, and enlargement of the nasal space with paradoxical nasal congestion. Among diseases responsible of secondary atrophic rhinitis, infective- and noninfective-granulomatous and autoimmune diseases may be advocated, even if they represent less than 1% of etiologies. This group of pathologies should be considered especially in patients without medical history of nasal surgery or radiation and in presence of systemic symptoms, such as low-grade fever, weight loss, and arthralgias. The most frequent autoimmune diseases resulting in atrophic rhinitis are granulomatosis with polyangiitis, sarcoidosis, and mucous membrane pemphigoid [1]. Among granulomatous infections, tuberculosis and syphilis are the leading reported causes of this group of rhinosinusitis [1].

An accurate anamnesis may highlight current or past unexplained skin lesions, arthritis, shortness of breath, or neurologic symptoms. In addition, history of travel in foreign countries and sexual promiscuity should be checked. Routine laboratory tests may underline high ESR and CRP values, anemia, and renal abnormalities, such as unexplained renal failure, proteinuria, and red cell casts. All patients with secondary atrophic rhinitis should undergo a Chest X-ray to rule out lung infiltrations or cavities and mediastinal lymphadenopathies. Presence of ANCA antibodies and QuantiFERON TB-test positivity should be checked; in presence of a suggestive history also VDRL, TPHA and HIV-test may be considered. A nasal biopsy aimed to perform histology and microbiological tests is usually required to confirm the diagnosis.

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2.1 Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis) represents, along with microscopic polyangiitis (MPO) and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome), the spectrum of diseases of anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV). This group of small-vessel vasculitis is characterized by common clinical features, presence of ANCA antibodies (in 60–90% of patients) and absence of immune deposits in the histologic samples.

2.1.1 Epidemiology and Pathogenesis

GPA is more common in older adults, with a peak in the sixth decade, although onset age may vary. The annual incidence is 2–13 cases/million per year and seems to be more frequent in Caucasian than in other ethnic groups [2]. Family history of autoimmune diseases, exposure to silica, and infective triggers or drugs such as propylthiouracil or methimazole are recognized risk factors for GPA development [3, 4].

ANCA antibodies target cytoplasmatic antigens, myeloperoxidase (MPO) and proteinase 3 (PR3). These antibodies are detected at first in indirect immunofluorescence (IFI), showing a perinuclear (p-ANCA) or cytoplasmic (c-ANCA) staining of neutrophil cytoplasm. This result is confirmed by enzyme-linked immunosorbent assay (ELISA) detecting antibodies targeting MPO (MPO-ANCA, i.e., p-ANCA, more common in microscopic polyangiitis) or PR3 (PR3-ANCA, i.e., c-ANCA, more common in granulomatosis with polyangiitis). ANCA antibodies may play a direct pathogenic role in GPA. After priming due to a proinflammatory event, MPO and PR3 antigens may be exposed on the plasmatic membrane and may be recognized by respective antibodies. This mechanism leads to a release of reactive oxygen species and granulation enzymes. During the acute phase, typical findings are necrotizing vasculitis with a self-destructing-neutrophil-rich infiltrate (*leukocytoclastic vasculitis*), sometimes with *fibrinoid necrosis* due to coagulation cascade activation and fibrin deposition. In the late phases of the disease, especially in the upper and lower airways, perivascular and extravascular granulomas may be found [5].

2.1.2 Clinical Features

The disease is characterized by granulomatous and necrotizing inflammatory lesions of upper and lower airways and is frequently associated with rapidly progressive pauci-immune glomerulonephritis resulting in a significant decrease in renal function.

2.1.2.1 ENT Involvement

ENT involvement is present in 75–98% of patients and represents the most typical organ impairment of GPA [6]. *Nose and paranasal sinuses* are the most frequently involved sites. End stage of atrophic rhinitis may induce a cartilaginous erosion (Fig. 2.1b) resulting in nasal septum perforation and the saddle nose (Fig. 2.1a). Since tissue damage depends also on a reduced blood intake caused by vessel inflammation, the most frequently affected area is the portion of nasal septum perfused by Kiesselbach's plexus. However, all structures of the nasal cavity, included mucosa, turbinates, and paranasal sinuses may be affected [7]. An *otologic* impairment may be present in 20–60% of GPA patients. Generally, it could display as a chronic mono or bilateral middle otitis, related to rhinosinusal involvement. Also, a chronic mastoiditis or an external ear involvement in the form of erythematous or ulcerating polychondritis-mimicking lesions could rarely be found [8]. Finally, 5–31% of patients may show an inner ear impairment due to cochlear vasculitis, manifesting with neurosensorial hypoacusia or vertigo; this presentation should also question the possible diagnosis of Cogan's syndrome. *Oral* manifestations are rare, mainly ulcerative stomatitis and hyperplastic gingivitis ("strawberry gingivitis"), the last one highly suggestive for GPA [9]. *Laryngeal* involvement is also possible. In 10–20% of patients, subglottic stenosis may be present, but this data could be underrated because patients with a less-than 75% stenosis are often asymptomatic; a more-than 80% stenosis can be life-threatening, thereby an early diagnosis is crucial and should require flexible endoscopy and CT scan.

2.1.2.2 Other-Than-ENT Involvement

Systemic symptoms, such as fever, asthenia, weight loss, and nonerosive arthritis, are present in 30–80% of patients. **Lung involvement**, present in 60% of patients, is characterized by fixed parenchymal nodules that could cavitate in half of the

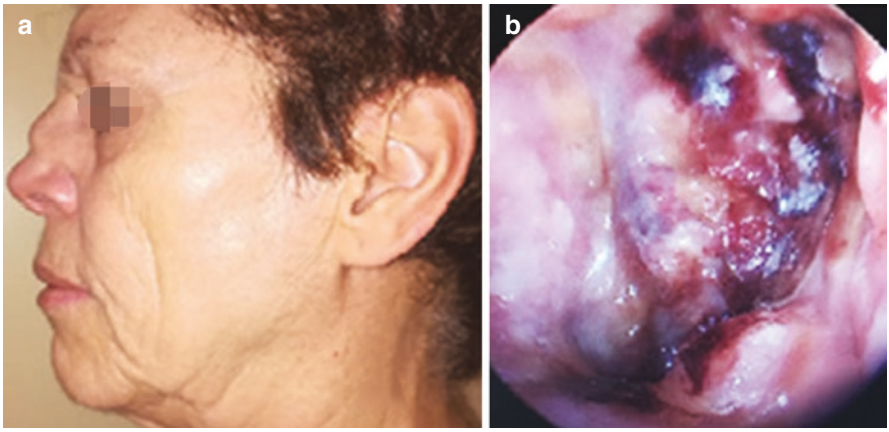

Fig. 2.1 (**a**) Saddle nose in a patient affected by granulomatosis with polyangiitis. (**b**) Extensive erosion with granulomatous appearance of the upper and lateral walls of the nasal pits and total lack of the nasal septum

Table 2.1 Red Flags for GPA suspect

In patients with atrophic rhinitis or other consistent ENT manifestations, a rheumatologic consulting should be considered in case of constitutional symptoms (fever, malaise, asthenia) paired with:
• Arthritis
• Sensory limb deficiency (especially inferior limb)
• Previous myocarditis history
In patients affected by atrophic rhinitis or other consistent ENT involvement, an urgent access to E.R. and an urgent rheumatologic must be indicated in case of:
• Severe anemia
• Acute renal failure, blood cast, and dysmorphic erythrocytes at the urinalysis
• Sensorimotor progressive limb deficit
• Progressive shortness of breath
• Palpable purpura and skin ulcers

cases, but also by alveolar hemorrhage, a severe complication burdened by high mortality rate (about 50%) in acute phase [10]. **Renal involvement** is the third most frequent organ involvement in GPA and is usually characterized by a rapidly progressive glomerulonephritis (17% of patients), showing with macrohematuria, progressive renal failure, and subnephrotic proteinuria (<3.5 g/day) due to a pauci-immune (immunofluorescence-negative) glomerulonephritis. A **neurologic impairment** could occur in one-third of patients, usually as multiple asymmetric mononeuritis, rarely as a symmetric sensorimotor polyneuropathy. Up to 50% of patients may show **skin** involvement, presenting with palpable purpura, focal skin necrosis, and ulcers. In some cases, urticarious vasculitis, livedo reticularis, or nodules may be found. Rare findings are **heart** (as rhythm disturbance, pericarditis, or myocarditis) or **eye** involvement (episcleritis, orbital granuloma, or pseudotumor).

Routine blood tests are usually unspecific. An elevation of inflammation markers and white blood cells is frequent. The presence of progressive renal failure along with subnephrotic proteinuria and sediment abnormalities (dysmorphic erythrocytes and red blood casts) should raise suspicion of renal damage.

Table 2.1 summarizes our suggested red flags for GPA suspect.

2.1.3 Diagnosis

Criteria for classification of Wegener's granulomatosis were developed in 1990 by the American College of Rheumatology. A patient shall be said to have Wegener's granulomatosis if at least 2 of these 4 criteria are present:

- Development of painful or painless oral ulcers or purulent or bloody nasal discharge;
- Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities;
- Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment;
- Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole).

The fulfillment of these criteria provides 88% sensitivity and 92% specificity in making diagnosis of GPA. Even though ANCA antibodies positivity (mainly c-ANCA) performs an eminent role in supporting diagnosis, it is not mentioned in these criteria; we would like to point out that since we are talking about "classification" (and not "diagnostic") criteria, diagnosis remains a prerogative of the clinician and depends on the comprehensive clinical picture.

The combined use of immunofluorescence and ELISA enables to detect ANCA in nearly all patients with active generalized GPA [11], but approximately one of five patients with active limited disease is ANCA negative [12]. PR3-ANCA (c-ANCA) are positive in up to 90% of patients, whereas 10–13% of GPA patients are MPO-ANCA positive (p-ANCA) [13].

GPA diagnosis should always be supported by histological sample if possible. Skin or renal biopsy should be preferred as sampling sites, whereas nasal mucosa biopsy might be avoided because of the paucity of achievable material leading to a high rate of false negatives [14]. Samples during florid phases of the disease are consistent with a necrotizing vasculitis of small vessels with neutrophil and monocyte–macrophage infiltrate, fibrinoid necrosis, and, rarely, granulomas [5].

2.1.4 Management

GPA therapy may change according to organ involvement and disease severity.

In patients with noble organ involvement, an induction treatment with high dosage of corticosteroids together with cyclophosphamide or rituximab is recommended; in case of life-threatening complications, such as alveolar hemorrhage or acute glomerulonephritis, plasmapheresis should be considered. Once remission is obtained, a maintenance treatment with mycophenolate mofetil, azathioprine, and methotrexate is performed [15]. In patients with mild-to-moderate conditions, an induction treatment with glucocorticoids, methotrexate, and mycophenolate mofetil is recommended. There is no recommendation about the initial steroid dosage: we suggest though an initial dosage of 0.5–0.75 mg/kg PDN equivalent with a tapering meant to reach 0.25 mg/kg by 3 months. In maintenance treatment, a combination of low-dosage glucocorticoids and azathioprine, mycophenolate mofetil, or methotrexate is recommended [15].

Despite not life-threatening, ENT manifestations are often resistant to immunosuppressive treatment. In patients displaying mainly ENT involvement, we recommend initial treatment with methotrexate at the weekly dosage of 0.2/0.3 mg/kg; we suggest rituximab in refractory patients, especially in ANCA-positive ones.

We also highlight that GPA patients displaying atrophic rhinosinusitis frequently show bacterial superinfections. Therefore, we also encourage daily nasal toilet with nasal irrigations and topical antibiotics in case of suspicious superinfection. Antibiotic treatment shall be provided orally in most severe infections [16].

2.2 Sarcoidosis

Sarcoidosis is a systemic disease featured by non-caseous granulomatous inflammation typically localized at inferior and superior airways.

2.2.1 Epidemiology and Pathogenesis

Sarcoidosis prevalence (about 10–20/100,000 inhabitants) varies according to ethnicity and the geographic region as it is more common in northern countries. Onset age is commonly young adulthood, peaking in 20-year-old people, although a second peak has been described in over 50 years old women [17]. A genetic predisposition related to innate and adaptive immunity genes polymorphisms has been suggested. Exposure to pesticides, beryllium and silica, and obesity are environmental predisposing factors, while smoke and female sex seem protective factors [18].

Sarcoidosis pathogenetic mechanisms are unknown. In a possible model for sarcoidosis pathogenesis, dendritic cells and macrophages recognize an exogenous antigen but are not able to eliminate it; so, the antigen is presented to naive T lymphocytes which differentiate in releasing INF-γ and TNF-α Th1 lymphocytes in order to increase macrophage microbicidal ability [19]. In turn, macrophages transform into epithelioid and giant multinucleated cells triggering granuloma formation. If this process succeeds in clearing the antigen, granuloma will solve, otherwise inflammation will become progressive and Th1 lymphocytes will switch to profibrotic TGF-β and IL-10 producing Th2 lymphocytes, leading to fibrosis [19].

2.2.2 Clinical Features

The most typical acute onset manifestation is Lofgren syndrome (clinical triad: erythema nodosum, bilateral hilar lymphadenopathy, polyarthritis–polyarthralgia), present in up to 30% of patients and Heerfordt–Waldenström syndrome (uveitis, parotitis, fever, at times facial nerve paralysis) that is rare (0.3% of patients) [20]. However, sarcoidosis frequently has an insidious onset with only lung involvement or more rarely with a different organ one.

2.2.2.1 ENT Involvement

ENT involvement is quite frequent during sarcoidosis, since it is present in up to 20% of patients [21] and can involve every organ.

Sinonasal sarcoidosis (SNS) is a chronic form of sarcoidosis often refractory to conventional therapies. It can be present in 1–4% of patients affected by sarcoidosis; it can have quite heterogeneous clinical manifestations and is rarely an onset symptom.

Lawson et al. [22] suggest to classify SNS in atrophic (crusts, mucosal erosions, nasal obstructions, epistaxis), hypertrophic (mucosal congestion with frequent

bacterial overinfection and bilateral polyps), destructive (loss of osteocartilaginous skeleton, septal and saddle nose perforation, middle and inferior turbinate destructions, and palatal fissures), and nasal widening (diffused or externally localized increase nose volume). The latter, different from lupus pernio, dramatically responds to steroid therapy coming back to original volume. A staging system has been suggested to take into account nasal structures' involvement to come up with proper treatment aggressiveness (Table 2.2) [23]. *Major or minor salivary glands* involvement can be assessed in 5–10% of patients and can be exhibited as an onset symptom even in Heerfordt syndrome (fever, uveitis, parotitis, possible facial nerve paralysis). More frequently parotid swelling is present along with xerostomia, but symptomatology might even be absent. Salivary glands biopsy is often burdened by false negatives, since only 38% of patients will show granulomas in palatine glands and 58% in labial salivary glands [24]. *Laryngeal* involvement in sarcoidosis is present in 0.5–1.4% of patients, and it is a rare finding if solitary or first organ manifestation. The most frequently involved region is supraglottic (80–85%), in particular epiglottis, arytenoid cartilages, and aryepiglottic folds since those structures are rich in lymphatic tissue. Subglottic involvement is present in 15–20% of patients, while vocal cord involvement is sporadic. The clinical pattern is unspecific and generally appears as a laryngeal mucosal edema that looks pallid and prominent, despite circumscribed exophytic lesions suspected for neoplasia have been described [24].

2.2.2.2 Other-Than-ENT Involvement

Systemic symptoms like fever and arthralgia are present in most patients; in patients affected by arthritis, ankle involvement is typical.

Sarcoidosis shows almost always (89–99%) **respiratory** involvement displaying with dyspnea, cough, pleural pain, or hemoptysis; most patients, anyway, can be asymptomatic. Chest radiographic findings are bilateral hilar lymphadenopathy (in 50% of cases) or heterogenous parenchymal lesions ranging from ground glass, diffuse reticular pattern, parenchymal consolidation, to fibrosis (Table 2.3). Rarely, pulmonary arterial hypertension can be present.

All patients with clinical suspicion of sarcoidosis shall undergo chest imaging, if possible high-resolution CT scan. Patients undergoing bronchoscopy exhibit in

Table 2.2 Staging system for sinonasal sarcoidosis according to Krispy

Stage 1	Mild, reversible disease without sinus involvement
Stage 2	Moderate, potentially reversible disease without sinus involvement
Stage 3	Moderate, potentially reversible disease with sinus involvement

Table 2.3 Chest radiography classification of pulmonary sarcoidosis

Stage 1	Bilateral hilar adenopathy without parenchymal involvement
Stage 2	Bilateral hilar adenopathy with parenchymal involvement
Stage 3	Parenchymal involvement (reticular opacities) with shrinking hilar nodes
Stage 4	Pulmonary fibrosis

bronchoalveolar lavage (BAL) typically lymphocytic alveolitis with high CD4/CD8 ratio. Once pulmonary involvement has been diagnosed, a spirometry should be performed to investigate a restrictive pattern.

Ocular involvement is frequent in sarcoidosis and can be present in 5–23% of patients, with symptoms that range from eye redness, photophobia, xerophthalmia, and rarely visual field deficit or impaired color perception. Uveitis is the most common manifestation (about 90% of ocular findings), but more severe clinical pictures such as optic neuritis or orbital tumor could be found.

Cutaneous involvement can be present in 16–32% of patients. The most typical manifestations are erythema nodosum and lupus pernio. Erythema nodosum is a septal panniculitis displaying with painful subcutaneous nodules covered by erythematous skin, usually located on limb extensor surfaces. Lupus pernio is characterized by indurate red-purplish plaques and fibrotic nodules on nose, malar region, and hand skin; these lesions have a destructive evolution and sometimes can deepen to erode the surrounding osteocartilaginous structures nearby, triggering ulcers, nasal septum perforations, and phalangeal lytic lesions [25]. Anyway, red-brown maculopapular rash is more frequently localized on the face, and small indolent subcutaneous nodules localized at extremities are more frequent.

Neurological involvement can be present in 3–9% of patients. The most common symptom is a facial nerve paralysis but other cranial nerve paralysis might also be present; peripheral somatic neuropathies are very rare. Skull base leptomeningitis is also possible and could evolve in encephalitis and chronic synechiae and hydrocephalus. Hypopituitarism (1% of sella turcica lesions) is also described and could display as diabetes insipidus or hyperprolactinemia-like symptoms.

Cardiac (arrhythmia, cardiomyopathy, heart failure, pericarditis, or valvular disease) and **renal** (nephrolithiasis secondary to hypervitaminosis D) involvement are also possible.

Laboratory findings include inflammatory markers elevation, leukopenia (5–10% of patients) with inverted peripherical CD4/CD8 lymphocyte ratio (because CD4 is sequestered in interested tissues to form granulomas). Other common findings are an elevation of the level of angiotensin-converting enzyme (ACE) and lysozyme (in 50–75% of patients), hypercalcemia/hypercalciuria and D hypervitaminosis.

2.2.3 Diagnosis

Since no definitive diagnostic test or criteria exist, sarcoidosis diagnosis requires a compatible clinical and radiological picture supported by exclusion of other causes.

Anyway, except for classical presentations (i.e., Lofgren and Heerfordt syndromes), diagnosis has to be confirmed by histology.

Histological findings in sarcoidosis are granulomatous inflammation characterized by multiple discrete predominantly epithelioid non-necrotizing granulomas. The granulomas are generally surrounded by few lymphocytes and a rim of mild dermal fibrosis (“naked granulomas”). Star-shaped (Asteroid bodies) and calcified

(Schaumann bodies) cytoplasmatic inclusions are also frequently found, though they are not specific to sarcoidosis [26]. The inflammatory site depends on the organ involved, and at lungs level, it is more commonly met along broncovascular fascia [27].

2.2.4 Management

Clinical treatment is chosen according to organ involvement and severity. Patients affected by pulmonary (50–80% of asymptomatic patients at stage I-II) and cutaneous (up to 60% of cases) sarcoidosis often reach spontaneous remission. Therefore, treatment is indicated in symptomatic patients with aggressive disease, aesthetic impairment, or radiological progression. However, in patients with cardiac, neurologic, ocular, or renal impairment aggressive treatment is preferred in order to decrease organ damage progression or fatal arrhythmia. First-line therapy is middle dosage (0.3–0.5 mg/kg to taper) oral corticosteroids. However, higher dosage therapy (up to 1 mg/kg to taper) should be started if acute respiratory failure, neurologic, cardiac, and ocular impairment is assessed. Low-dose steroid therapy should be continued for at least 6 to 8 months to prevent relapses. Refractory diseases should be evaluated for immunosuppressive treatment. Most used DMARD is generally methotrexate, while mycophenolate mofetil, azathioprine, rituximab, or anti-TNF are reserved to those patients with the most severe organ involvement or poorly methotrexate responsive [28].

Upper respiratory tract sarcoidosis undergoes spontaneous remission in few cases (10% of patients); therefore, these patients require generally topical, systemic, or surgical treatment. ENT standard therapy includes nasal irrigations, topical steroids, and antibiotics for acute super-infections. Topical (inhalators or nasal) steroids monotherapy is rarely effective in achieving the complete control of nasal and laryngeal symptoms, but it could be useful in combination with systemic therapy or in maintenance therapy. Intralesional injectable steroid instead allows rapid symptoms improvement and reduces systemic steroidal requirement. Systemic treatment follows the general principles given for other organ diseases, but since often organ involvement is chronic, we suggest an earlier use of DMARD (especially methotrexate) as steroid-sparing therapy. Minimal invasive endoscopic surgery is reserved to patients not responsive to medical treatment; surgical excision with CO_2, laser, and microdebriders can be employed for circumscribed lesions [29].

2.3 Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is an uncommon autoimmune blistering disease, characterized by autoantibodies-mediated damage to basement membrane zone. It could be considered a variant of bullous pemphigoid with a predilection for mucosa and with a scarring evolution.

2.3.1 Epidemiology and Pathogenesis

MMP is a rare disease, with an estimated prevalence of 2 cases/million for MMP in Europe. It is considered a disease of elderly age, occurring most frequently in the sixth or seventh decade with a predilection for female people [30]. Exposure to infections such as viral hepatitis, *Cytomegalovirus*, *Helicobacter Pylori,* and *Toxoplasma Gondii* and to drugs, especially oral hypoglycemics dipeptidyl peptidase-4 inhibitors may play a role in outbreaking of blistering diseases, as might a genetic predisposition [31, 32].

MMP is caused by antibodies-mediated damage against antigens of basement membrane zone (such as BP180, BP230, Laminin 332, α6β2-integrin, and Type VII collagen), in mucosa and skin, resulting in destruction of structures mediating cellular adhesion and in separation of epithelium from subepithelial tissues.

2.3.2 Clinical Features

MMP, also known as cicatricial pemphigoid, is characterized by relapsing-remitting tense vesiculobullous lesions eroding and evolving to scarring ulcers. MMP can be distinct from bullous pemphigoid thanks to a higher prevalence of mucosa than skin involvement and the tendency to scarring after the bulla rupture. The main impaired mucosal sites are oral cavity (85%) and eye conjunctiva (64%), but also genital, esophageal, and bronchial mucosa; the skin may be involved in 25% of patients. Because mucosal bulla tends to rapidly break, the detection of intact blister is quite uncommon; therefore, diagnosis could be difficult in patients without skin involvement [33].

2.3.2.1 ENT Involvement

ENT symptoms could involve about 35% of patients, complaining especially about nasal symptoms. Atrophic rhinitis is the most frequent nasal lesion found in physical examination, especially on the septum and turbinate, possibly associating with crusting in 25% of patients, whereas the detection of intact bulla is rare. Chronic disease may lead to sequelae as severe scarring, stenosis and synechiae and eventually to death. Laryngeal involvement could also be asymptomatic, appearing only with acute dyspnea caused by severe stenosis [34].

2.3.3 Diagnosis

MMP diagnosis requires a suggestive clinical picture and supporting laboratory and/or histologic data. MMP should be questioned in older patients presenting with diffuse mucositis involving more than one head and neck mucosal district; the concomitant presence of anal or genital mucositis and unexplained skin tense blisters must raise the suspicion. The detection of autoantibodies could support the diagnosis. ELISA testing of serum for basement membrane zone antibodies other than

BP180 and BP230 primarily is performed only in research laboratories, limiting the sensitivity of this testing mode in the MMP population.

The use of human basement membrane zone-split skin and/or concentrated serum raised the indirect immunofluorescence sensitivity to about 84% [35].

Skin biopsies should be performed to confirm the diagnosis, preferably on an intact vesicle including the immediately adjacent tissue. Common histopathologic H&E findings include epithelial–subepithelial split with an inflammatory cell infiltrate rich in eosinophils, lymphocytes, and neutrophils.

Direct immunofluorescence (DIF) is the most sensitive supportive diagnostic test for MMP diagnosis. The typical DIF feature in MMP is linear IgG and/or linear IgA and/or linear C3 staining along the basement membrane (70–100% of cases).

2.3.4 Management

Ocular, genital, and laryngeal involvement frequently leads to irreversible scarring, so early detection and treatment must be directed to prevent or delay severe sequelae (such as blindness and stenosis).

Patients with involvement of oral mucosa and/or skin may be managed initially with local treatment (topical or intralesional steroids and topical tacrolimus), reserving systemic drugs to therapeutic failures. Patients with ocular and laryngeal impairment, in contrast, need an early aggressive treatment with systemic drugs. Life-threatening disease patients should receive an induction treatment with high-dose corticosteroids. The most use dosage is oral prednisone 1 mg/kg dosage with subsequent tapering, but some authors propose a more aggressive treatment with pulse IV steroids (until 1 g/day). Immunosuppressive steroid-sparing therapy should be associated: the main employed drugs are azathioprine, mycophenolate mofetil, dapsone, and methotrexate. The usage of intravenous immunoglobulins or rituximab should be considered in refractory patients [36].

2.4 Tuberculosis

Mycobacterium Tuberculosis is a member of the mycobacteria family, a *genus* of bacteria featured by a mycolic acid–rich cell wall and by particular staining properties (Gram staining resistance and Ziehl–Neelsen staining) and antibiotic resistance.

2.4.1 Natural History of Disease

Since *M. Tuberculosis* spread is aerial, tuberculosis involves classically lower and upper airways. *Mycobacteria* arrive in alveoli inside small droplets (5–20 μ) and they are phagocytized by alveolar macrophages in which they can survive in 5–10% of cases (primary disease). In immunocompetent patient, monocytes and macrophages are recruited from the bloodstream and Th1-dependent cell-mediated

immune response is brought about with tubercle formation (initial granuloma). In this phase, granuloma can expand to pulmonary parenchyma (Ghon's focus, typically subpleural location) and bacilli can migrate invading adjacent lymph nodes (Ranke complex). After 2–10 weeks from transmission, immune response is wholly manifested and infection is contained in granulomas that undergo caseating necrosis. In this phase, the **infection** is **latent**, but can reactivate as the host immune responses weaken. If cell-mediated immunity is not efficacious, its continuous activation can trigger both adjacent parenchymal destruction with tubercular rupture into airways and extrapulmonary tuberculosis for lymphatic–hematogenous spread.

2.4.2 Epidemiology

In 2019, extrapulmonary tuberculosis has represented 15% of TB cases notified to the WHO; such phenomenon has increased in the last years in response to the higher number of patients having immune depression-related conditions. Moreover, some statistics demonstrate extrapulmonary findings in up to 50% of all cases of TB.

2.4.2.1 ENT Involvement

Virtually all organs can be involved but the most frequent extrapulmonary sites are lymph nodes, pleura, and skeletal system. Head and neck tuberculosis is generally rarer and comprises 2–6% of extrapulmonary TB and less than 1% of all TB cases. Mainly, laterocervical lymph nodes and larynx (about 95% cases) are interested, while rarer locations are nasal cavities and rhinopharynx. The latter two however are often primitive sites and are associated with pulmonary and systemic symptoms only in 25–30% of cases [37].

Nasal tuberculosis may be caused, together with lymphohematogenous spread from different sites, by bacilli inoculation or traumatic digital inoculation [38]. Patients affected by nasal tuberculosis generally exhibit jugular lymphadenopathy, nasal and nonspecific auricular symptoms (nasal obstruction, rhinorrhea, posterior nasal drainage, hearing loss, tinnitus, otalgia). The endoscopic and radiological aspects are also nonspecific ranging from a normal mucosa up to polypoid, ulcerated, and leukoplastic masses [39]. The most frequently involved area is the nasal septum near the mucocutaneous junction and posterior septal extremity [40]. When the lateral walls are interested, inferior turbinates are then more frequently involved. A septal perforation may also be present, whereas the nasal floor is almost always spared and posterior nares are rarely involved. A spread of infection from nose to sinuses may occur, involving ethmoid, sphenoid, frontal, or maxillary sinuses; also, orbit may be hinted through lacrimal duct [41].

2.4.3 Diagnosis

Tuberculin skin test (Mantoux intradermal reaction) and interferon-gamma release assay (IGRA) can support TB investigation, despite they show an inadequate

accuracy in patients with extrapulmonary tuberculosis [42]. Nasal tuberculosis diagnosis has to be supported by mucosal biopsy histological and microbiological assessment. Epithelioid granuloma with giant cells and caseous necrosis is the histological hallmark of TB, although it is not observable in all patients.

It is necessary to confirm the diagnosis by bacterial DNA research with polymerase chain reaction (PCR), bacterioscopic test and culture.

In patients affected by nasal TB, pulmonary and systemic disease has to be ruled out.

Chest X-ray is mandatory in all patients, while in those displaying respiratory symptoms at history taking (productive cough, hemoptysis, and/or systemic symptoms (weight loss, low-grade fever), CT scan shall be considered.

Since primary nasopharyngeal tuberculosis is far more common than secondary, other organ site involvement investigation shall be driven by clinical suspicion rather than screening. In patients affected by nasopharyngeal TB, innate or acquired immunodeficiency conditions should be excluded by evaluating complete blood count test (leuko/lymphopenia), immunoglobulins classes and subclasses, lymphocytes subpopulations, and by ruling out HIV co-infection.

2.4.4 Management

Nasopharyngeal tuberculosis treatment is no different from pulmonary one and requires as first-line drugs rifampicin (R), isoniazid (H), ethambutol (E), and pyrazinamide (Z). The standard drug regimen consists of an induction phase with HRZE for 2 months followed by a maintenance phase with HR for the four following months. This regimen should be modified in case of multiorgan dissemination or in case of CNS or skeletal involvement by lengthening treatment duration to 12 months. Regimen can also be modified according to antibiogram in case of germs multidrug resistance (MDR) or extensively drug-resistance (XDR).

2.5 Syphilis

Syphilis is an infective disease caused by Spirochetes, *Treponema Pallidum*. Syphilis is mainly a sexual transmitted disease, although a mother-to-child transmission through the placenta or birth canal is possible.

2.5.1 Epidemiology

WHO estimated, in 2016, a syphilis prevalence of 19.9 million, of which 6.3 million were cases diagnosed in the last year [43]. Diffusion in higher in non-Western countries and in young males, especially in HIV-positive and homosexual ones.

2.5.2 Clinical Presentation and Natural History

After 2–6 weeks of incubations, a **primary lesion** appears at treponema inoculation site. It is an indolent ulcer with elevated hard margins (chancre or syphiloma) flanked by locoregional lymphadenopathy. The primary lesion undergoes spontaneous resolution after 4–8 weeks. This phase can sometimes be asymptomatic. In 25% of cases, *Treponema* can spread systemically from inoculation site and triggers, after 4–10 weeks, a **secondary syphilis** that might spontaneously resolve in few weeks. Clinically, constitutional symptoms (fever, malaise, anorexia, arthralgia, weight loss), lymphadenopathies and skin manifestations may be present; the classical eruption is a diffused and symmetrical maculopapular rash at trunk, extremities, palm, and soles but pustular rush and elevated gray-whitish mucosal lesions called flat condylomas may be present as well. In this phase, articular (arthritis, osteitis), gastrointestinal (hepatitis with elevation in alkaline phosphatase and weak elevation of transaminases), and renal manifestations (mild proteinuria, nephrotic, or nephritic syndrome) could show. Spirochetes can be identified in cerebrospinal fluid and determine neurological (meningitis, meningovascular disease) and ocular symptoms (panuveitis, chorioretinitis), even at this stage. Nontreated early patients can progress toward **tertiary syphilis** (1–30 years after contagion) which has the most severe manifestations such as syphilitic aortitis (generally descending aorta aneurysm), tabes dorsalis (a myelo-meningo-radiculitis that affects posterior roots and triggers sensitive ataxia and neuropathic pain) and syphilitic gummas (granulomatous lesions that tend to ulcer and that can affect any organ, almost exclusively in HIV-positive patients).

Congenital syphilis is nowadays present almost exclusively only in south of the world countries, and it has anyhow decreased by 39% in last decades. Mother-to-child transmission can occur during all pregnancy duration, but it is mainly placental. Risk increases according to disease staging since it is higher in primary and secondary phases (>80%) and lower in the latent phase. The early congenital syphilis (within 2 years) can trigger intrauterine death, low birthweight, lymphadenopathy, splenomegaly, and pemphigus syphiliticus (bullous rash). In late congenital syphilis (4–20 years), interstitial keratitis, hearing loss for VII cranial nerve malformation, and dental anomalies (Hutchinson's triad) can be present.

2.5.2.1 ENT Involvement

Oral cavity and oropharynx can be involved during all syphilis stages. Primary syphilis must be taken into account with oral cavity necrotic ulcers accompanied by homolateral lymphadenopathy [44]. During the secondary phase, whitish maculae covered by fibrinous pseudo membranes, mucosal plaques, or papules (condyloma latum), at times eroded or ulcerated can be present [45].

Nasal syphilis is rather uncommon but is possible in all stages. Atrophic rhinosinusitis may be found in secondary and tertiary stages.

Primary chancre is reported to occur in the mucocutaneous junction of nasal vestibule or the anterior part of the septum. In secondary syphilis, acute rhinitis may be present with snail track discharge, along with fissures in the vestibule. The third stage is the most characteristic, presenting with diffuse mucosal swelling and ulcerations

or localized gummas. Gummatous deposit may be found in any portion of the nose, but the most commonly involved site is the septum, especially the cartilage–bone junction, resulting in a perforation. In the diffuse form, there is inflammation starting most frequently in the submucous tissues, extending both to the surface and the deeper tissues with subsequent degeneration, resulting in superficial or deep ulcerations, eventually involving also cartilaginous and bony structures leading to perforation. The characteristic "saddle nose" may be present in both forms [46].

Nasal involvement is frequent during congenital syphilis. At early phase, it typically develops within the third month and is featured by a nasal drainage initially watery, then progressively blood-tinged or purulent. Since the drainage is persistent, it is contagious and can transmit the infection by direct contact. At late phase, saddle nose deformity can occur for support structure failure [47].

2.5.3 Diagnosis

Diagnosis suggested by clinical suspicion must be supported by microbiological findings of *Treponema* on indirect tests (treponemal and nontreponemal) performed on serum and direct tests on involved biological samples.

Nontreponemal indirect tests (VDRL, RPR, TRUST, TP-EIA) are based upon serum positivity of patients affected to cardiolipin-lecithin-cholesterol antigen. Those are not specific tests but they are cheap and relatively sensitive and therefore are used as screening tests. Treponemal indirect tests (TPHA, MHA-TP) detect specific antibodies for the microorganism and are used to confirm.

Direct tests allow direct visualization of microorganisms on the histological sample of the lesion. The germ can be visualized with darkfield microscopy and direct fluorescent antibody test (DFA). However, the latter test is not available in ordinary laboratories. PCR for *T. Pallidum* DNA is more diffused and shows elevated sensitivity and specificity.

2.5.4 Management

The treatment of choice during all syphilis phases is antibiotic therapy with penicillin, mainly Penicillin G IV. The choice of Penicillin G–type (benzathine, aqueous procaine, and aqueous crystalline), dosage, and length of treatment depends upon the staging and clinical manifestations. An alternative therapy in patients with allergy to β-lactam antibiotics could be doxycycline or azithromycin [48].

2.6 Other Autoimmune and Granulomatous Causes of Atrophic Rhinitis

Other infective causes of atrophic rhinitis can be leprosy and some fungal infections such as actinomycosis [47]. Some cases of atrophic rhinitis during Sjogren's syndrome and Crohn's disease have been mentioned in literature [49, 50].

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Iatrogenic Atrophic Rhinitis: Post-Nasal Surgery or Empty Nose Syndrome (ENS)

3

Peter Michael Baptista Jardin, Marta Álvarez de Linera-Alperi, and Paola L. Quan

3.1 Introduction

Atrophic rhinitis (or rhinosinusitis) (AR) is a complex syndrome associated with progressive atrophy of the nasal mucosa and underlying bone [1]. It is a disease of debatable and often unproven etiology [2]. Some consensus exists [3] around the general theory that it can originate either as a primary form (as discussed in previous chapters) that is mostly related to bacterial colonization [4] or as a secondary consequence of traumatic and inflammatory stimuli to the nasal mucosa. Both situations lead to a significant impairment in the quality of life of the patient [5]. The purpose of this chapter is to conduct an in-depth exploration of the form of atrophic rhinitis that occurs after sinonasal surgical intervention. This type of atrophic rhinitis will be referred to as "empty nose syndrome" (ENS). Specific etiologies and epidemiology and proposed theories for pathophysiology will be discussed. Typical clinical manifestations, as well as features that are distinct from the primary form, will be reviewed. Finally, we seek to provide a guide for the diagnosis and management of this chronic pathology according to existing evidence in the literature.

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3.2 Epidemiology

Secondary atrophic rhinitis is a rare clinical condition [6] that occurs as a complication of nasal or sinus surgery or due to medical intervention, craniofacial radiotherapy, or traumatic or chemical injury [1]. It can occur months or years after a specific procedure. Its exact incidence is unknown [7], as there are no formal studies in the literature focused on an epidemiological description. Postsurgical secondary atrophic rhinitis has often been referred to as "empty nose syndrome" (ENS), due to a common defining clinical finding: a paradoxical, subjective feeling of blocked (or absent) airflow that contrasts with the persistence of permeable nasal cavities on examination as well as normal values upon objective nasal obstruction measurements [8]. Although the term "ENS" was initially used to describe the radiologic findings in patients after a turbinectomy, it now constitutes a distinct syndrome of its own [9]. Due to the lack of consensual definition and the wide variety of the current established criteria (clinical, endoscopic, radiological, and histological), revisions of classifications are now expanding to include "not elsewhere classified," or "NEC" types [10].

Some authors have concluded in their work that ENS is an iatrogenic disease produced by surgery [7, 11]. Older series of turbinate surgery fail to report cases of this syndrome [6, 12]. Inferior turbinectomy is currently recognized as the most relevant subtype of nasal intervention associated with secondary atrophic rhinitis [8].

3.3 Pathophysiology

The exact pathophysiology of the disease remains unknown. It is believed that there is:

1. a decrease in the ability of the nose to humidify and heat the air,
2. a deterioration in mucociliary function, and
3. a lack of perception with proper activation of the cold receptors TRPM8 (responsible for the perception of nasal patency) [13].

The sensation of nasal patency is dependent on adequate mucosal cooling as well as on a sufficient number of adequately functioning TRPM8 receptors. Nasal mucosal cooling is a result of conductive heat loss, driven by a temperature gradient, and evaporative heat loss [5]. Variables that affect these essential components of mucosal cooling include nasal surface area and airflow characteristics within the nasal cavity. In the nose, particularly the inferior turbinates act to create turbulence within the nasal cavity. Turbinectomy has been described as the trigger, capable of damaging the neurosensory receptors responsible for pain and temperature sensations [14] and is more related to extensive turbinate tissue loss [8, 15]. Paradoxically, however, this disease can also be seen in patients who have lost only a small percentage of their turbinate tissue, with a normal appearance in size on imaging [8].

The loss of mucosal tissue after a turbinectomy produces a decrease in the evaporation of mucosal fluid by airflow, leading to interference with signal transduction and thus, producing an irregular perception of nasal breathing, changes in lung capacity [16], a subjective sensation of congestion [5], and turbulent nasal airflow due to a reduction of overall surface area of the nasal passages. Mucosal cooling is compromised, and so the sensation of nasal patency is not elicited [17, 18].

3.4 Clinical Manifestations

Atrophic rhinitis, in general, should be suspected when a patient describes a persistent feeling of nasal obstruction or difficulty in perceiving airflow [2], accompanied by the presence of abnormally wide nasal cavities on exploration [6, 19]. This defining clinical feature sheds light on the fact that this disease relies on clinical diagnosis and is dependent mostly on subjective symptoms referred by the patient rather than objective and measurable tests [8]. According to some authors, the main clinical manifestations of the primary form of this syndrome could be summarized as follows: nasal dryness, dyspnea or suffocation, paradoxical nasal obstruction, and usually crusting, generally without foul odor [5, 11]. Most patients who request medical help may describe a sensation of congestion and paradoxical nasal obstruction [20]. Anomalies of olfaction, pain or facial pressure, and intermittent episodes of epistaxis may also appear with this condition, although its prevalence is much lower [2, 20]. Extranasal symptoms include dyspnea, generalized fatigue, and sleep and mood disturbances [2]. Usually, patients may describe the onset of symptoms months or years after surgery, particularly after inferior and medial turbinate surgery [20].

ENS is often accompanied by signs of inferior or medial turbinate resection, as shown in CT scans or by the endoscopic view (Figs. 3.1 and 3.2).

Shah et al. (2016) [11] described the three subtypes of ENS currently known: ENS-inferior turbinate (ENS-IT), ENS-middle turbinate (ENS-MT), and ENS-both (middle and inferior turbinectomy). Although the symptoms are very similar

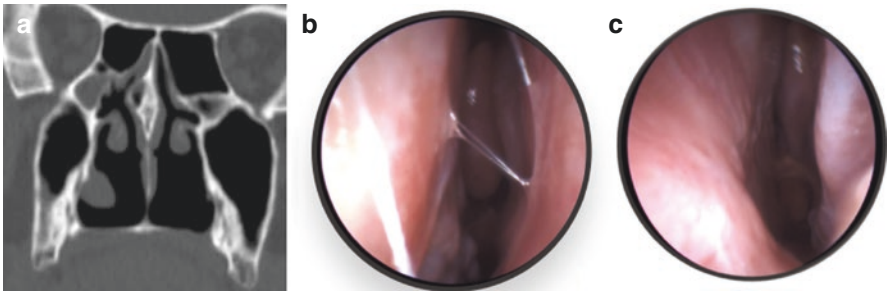

Fig. 3.1 (**a**) Coronal projection of CT scan with over-resection of inferior turbinate right nostril complete resection left nostril. Endoscopic view of left nostril. (**b**) Left anterior nostril (**c**) Middle area of left nostril

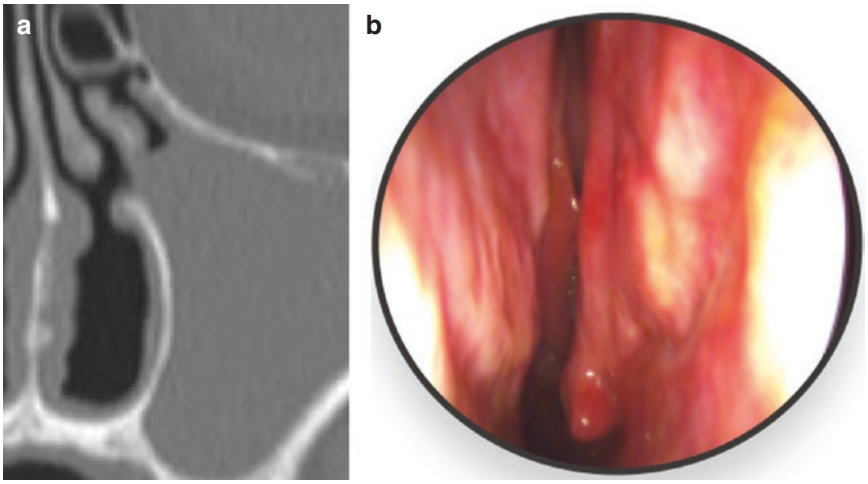

Fig. 3.2 (**a**) Coronal section of CT scan with complete resection of left inferior turbinate. Please observe natural irregularities that occur in the septum due to a natural tendency of compensation to avoid high amounts of flow (**b**) Endoscopic image of this same area

between these three entities, ENS-MT is more often associated with pain at the nasal level, possibly related to airflow alterations on the sphenopalatine ganglion mucosa [21]. Houser [21] also described a fourth possible entity named ENS-Type, in which airway appearance is healthy, while symptoms remain similar to those observed in other subgroups. Remarkably, patients with chronic rhinosinusitis seem to show less severe symptoms after inferior turbinectomy, probably due to the post-surgical hypertrophy of the nasal septum [12].

This disease presents a frequent association with psychiatric factors and neuropathic disorders of the head and neck, which can sometimes explain the fact that patient complaints are mostly subjective. There have been descriptions in which the symptoms may lead to suicidal ideation [22], and there is a higher incidence of concomitant complaints such as fibromyalgia, migraine, or irritable bowel syndrome [9].

3.5 Evaluation and Diagnosis

It is important to remember that ENS is mainly a clinical diagnosis, and very often, a diagnosis of exclusion [23]. No objective findings on the physical examination have been defined as typical or pathognomonic for ENS [23]. Its detection relies heavily on an adequate interpretation of symptoms by the clinician, without adequate support from reliable laboratory or exploration tests.

It remains essential to conduct nasal endoscopy to observe the size of the nasal cavity, from the anterior area up to the choanae, determining changes of the nasal and nasopharynx mucosa, such as pallor, ulcers, crusts, dryness, and tissue

dystrophy [1]. Imaging studies may allow recognition of the loss of tissue due to previous surgical procedures. Turbinate size may not always be reduced, and despite the fact radiographic imaging (generally a CT scan) may orient the clinician, its specificity as a diagnostic tool cannot be ascertained entirely.

Rhinomanometry or acoustic rhinometry generally may show little or no objective nasal obstruction and low or absent airflow resistance [8].

Houser [8] proposed the use of an alternative test to evaluate the patient's sensation of dry nose and capacity for improvement by applying saline-moistened cotton balls within the patient's nasal cavity. This test was validated posteriorly by Thamboo A [24] to be useful in the office. The application of local moisture seems to increase nasal resistance and to restore airflow distribution, which explains its effect in symptomatic patients [25].

In 2016, a new useful, and reliable tool for diagnosis, based on a questionnaire termed *"Empty Nose Syndrome 6-item Questionnaire (ENS6Q)"* [26] was validated.

Other assessment tests (laboratory studies, radiologic images, microbiological, and histopathological evaluations) have not proven themselves able to reach an accurate diagnosis. They are generally meant to exclude other diseases of a similar clinical spectrum. The histopathological examination has shown similarities in diverse kinds of atrophic rhinitis, with similar features in epithelial and vascular architecture, even if the independent origin of the disease [3]. However, a recent study [27], but with a limited amount of patients, showed evidence that ENS presented significantly more squamous metaplasia, a higher rate of submucosal fibrosis, a lower submucosal gland number grading, a unique histological change called goblet cell metaplasia, with intact preservation of ciliated cells and goblet cells of the respiratory epithelium, and also a significantly lower expression level of TRPM8.

Bacteriology is also recommended in case of crusting and suppuration; it allows specific antibiotic therapy.

3.6 Differential Diagnosis

Allergic rhinitis, atrophic rhinitis, and ENS are completely different nasal diseases that may have in common the presence of nasal obstruction. However, a meticulous history and examination with particular emphasis on the possible trigger allow a correct diagnosis.

Allergic rhinitis is considered a genetic IgE-mediated inflammatory disease and has determined features that will not be discussed here.

The description of an inflammatory atrophic disorder with loss of turbinate and mucosal tissue caused either by infection (primary AR) or due to trauma, radiation, granulomatous disease (secondary, non-iatrogenic AR) will be considered as AR.

If a paradoxical nasal obstruction occurs after turbinectomy, the syndrome will be described as an iatrogenic disease, orientating the main diagnosis to ENS. However, histological examination is recommended in order to attempt a differentiation between AR and ENS [11].

3.7 Treatment

3.7.1 Prevention

It is known that turbinate surgery is an important adjunct to functional and cosmetic rhinoplasty [28] and diverse degrees of resection (total, subtotal, and partial) of components (bone, submucosa, and mucosa) to increase the size of the nasal airway have been described.

Minimally, invasive surgery on the turbinate that preserves the nasal mucosa is key to achieving optimal results; it allows widening the nasal passages while preserving cool thermoreceptors within the mucosa and minimizing overall injury to the nasal mucosa.

Although there are diverse techniques to reduce the size of the turbinate, with descriptions that include (a) complete resection, (b) partial resection, (c) submucosal resection, and (d) bone resection with the conservation of tissue, also diverse types of devices (laser, microdebrider, diathermy, coblation, quantic molecular resonance, etc.), studies show that minimal submucous resection or submucosal reduction has better outcomes with fewer complications [29–36]. In the last two decades, endoscopic endonasal approaches (EEA) have been used to reach the ventral skull base. The sinonasal corridor offers direct access to this area, avoiding the use of open approaches like craniotomy and brain retraction. In these procedures, a frequent resection of the middle and superior turbinates and posterior septum to provide space for instrumentation has been observed. However, these patients seldom develop ENS symptoms [37] regardless of the expansiveness of the procedure. Those who develop it have impaired airflow at the level of the inferior turbinate. Therefore, conservation of at least part of the inferior turbinate may diminish the possibility of ENS.

3.7.2 Medical Therapy

Conservative management is recommended as first-line treatment for the management of ENS in general [6, 38]. Nasal cavity moisturization with the use of hydrating ointments and saline washes and sprays, frequently used during the day, tends to avoid dryness, crusting, and pain [39]. Menthol solutions or ointments may be of benefit in some cases, through direct stimulation of those available residual TRPM8 receptors related to the perception of nasal cooling [13, 40].

Adjuvant antibiotic therapy and local nasal corticoid treatment should be added when complications justify its use.

As mentioned earlier in the chapter, patients suffering from ENS have a significant, concomitant, documented anxiety, depression [41, 42], and somatic disorders that may impact their behavior and their family relations. Therefore, there might be a need for consultation with psychology or psychiatry specialist for treatment with cognitive behavior therapy (CBT) [9, 41].

Failure to treat the psychiatric comorbidities of ENS will compromise the results of any of the medical and surgical treatments offered to these patients.

3.7.3 Surgical Repair

Many procedures have been tried to improve outcomes; these include treatments used in atrophic rhinitis and transferred to ENS, like the use of nasal flaps or fabricated plugs to close the nasal corridor [43, 44] temporarily. However, data is very sparse in this aspect.

Recent reviews suggest surgical treatment as an option for endonasal repair [6]. Most procedures aim to restore turbinate and mucosal volume to meet the normal functions of humidification and warming of inhaled air [21].

These procedures should be viewed as turbinate reconstruction procedures. Often turbinate reconstruction may not be feasible; in these instances, adding bulk along other nasal surfaces (septum, lateral walls) under the mucosa may improve outcomes. Surgical intervention planning should be based on the results of the cotton test, which helps to identify sites of deficient turbinate tissue.

Various materials and techniques have been used for submucosal grafting with encouraging results [45–48]. These could be classified into (1) temporary fillers, (2) acellular dermal allografts, (3) autologous cartilage, and (4) synthetic implants.

3.7.3.1 Temporary Fillers

There have been reports of the off-label use of cross-linked hyaluronic acid (Juvederm, Allergan, Inc., Irvine, CA). Its injection in the submucosa has been described as a minimally invasive option in patients with ENS [46]. Other similar products have been used originally for temporary vocal cord augmentation, like carboxymethylcellulose/glycerin gel (Prolaryn® Merz, Raleigh, NC), with good results [49] reported. The aim of the injection site was the inferior meatus. There was an improvement in the ENS6Q and Sino-nasal Outcome Test-22 (SNOT-22), Patient Health Questionnaire-9 (PHQ-9), and depressive (Generalized Anxiety Disorder-7) tests.

The use of fillers is subject to reabsorption and loss of effect (2–12 months). A complete explanation should be provided to the patient as these fillers have not been approved for their use in this matter, and a complete verbal and written informed consent should be sought. The injection may be placed under local anesthesia, with precaution to avoid intravascular injection, which can (theoretically) lead to thromboembolic complications.

These procedures can serve as a previous step before the placement of permanent material and allow the perception of clinical and psychological benefit. It should be performed using the sites where the patient has noted the most significant improvement with the use of the cotton test.

3.7.3.2 Acellular Dermis Allografts and Xenografts

Diverse publications have described the use of acellular dermis allografts (AlloDerm, Allergan, Inc) and xenografts (porcine submucosal intestine) for the treatment of ENS [8, 20, 45, 50].

These grafts are placed in the lateral wall, providing a pocket for insertion under endoscopic view.

Clinical efficacy has shown good results, although resorption and breakdown have been reported, especially in xenografts [51]. Moreover, these grafts are expensive.

3.7.3.3 Autologous Cartilage

These grafts are harvested from a nearby site in the patient. They have the advantage of minimal rejection, as well as the amount of material that can be retrieved. The semirigid consistency allows reshaping and easier placement in a pocket over the preferred area. Reports show different sites of extraction of cartilage (ear, nasal septum, or rib) [47, 52, 53]. Good results have also been reported in all parameters of quality of life.

There has been a recent report [54] of the injection of autologous stromal vascular fraction to regenerate the area, in a small number of patients. At 6 months, they reported that there was no significant difference in pre and postoperative SNOT-25 scores; however, there was a decreased level of inflammatory cytokines, such as interleukin-8, in nasal secretions.

3.7.3.4 Synthetic Implants

The use of synthetic implants has been described in diverse publications. Even though the material is nonreactive, there is the possibility of rejection due to its foreign body nature. In nasal reconstructive surgery, diverse materials have been used such as Silastic [50] (hydroxyapatite [55], Gore-Tex [8], Plastipore [56], Nonporous β-tricalcium phosphate, [57], porous polyethylene (MedPor, Stryker Corporation, Kalamazoo, MI) [58, 59]. The extraction of the implant may be complicated if extraction is warranted. Good short-time results have been reported.

Surgical therapy has received more acceptance with time since the evidence of favorable outcomes both in nasal symptom scores and in comorbid mental health domains has been reported [22, 60].

Leong [22] reviewed the results of patients suffering from ENS that received a transnasal surgical intervention with implant material that was secured within a submucosal pocket. A significant improvement was seen in most patients in the Sino-nasal Outcome Test (SNOT)-20 and SNOT-25 scores at follow-up. The most significant improvement was observed in ENS symptoms and psychological issues. SNOT scores improved by 3 months post-surgery, and this trend continued over time, although available data was limited to only 12 months follow-up. Unfortunately, not all patients had the same excellent results.

Indications should, in all cases, be carefully considered; we recommend neuropsychological counseling ahead of any decision to operate, given the possible psychological impact of surgical failure.

Sphenopalatine ganglion nerve blockage could be considered as an adequate treatment in those patients diagnosed with ENS-MT who associate neurological symptoms [12] in selected cases.

3.8 Conclusions

Nasal surgery is usually performed to treat nasal obstruction to increase airflow. However, aggressive nasal surgery has the potential to reduce the nasal air conditioning capacity, with the possibility of producing significant disturbances. Sometimes over-resection of structures, instead of improving breathing, produces iatrogenic atrophic rhinitis that has been termed "empty nose syndrome (ENS)."

This syndrome should be suspected in any patient referring sensation of paradoxical nasal obstruction, especially if there is a previous history of any type of turbinate surgery. Although some complementary diagnostic methods could support the diagnosis, the combination of accurate medical history and an adequate physical examination should be considered the best diagnostic tool.

Treatment is based on the prevention of over-resection of turbinates. When diagnosed, conservative management is recommended with nasal cavity moisturization with the use of hydrating ointments and saline washes and sprays, frequently used during the day, to avoid dryness, crusting, and pain. Surgical treatment has shown to be an option to restore turbinate and mucosal volume, as well as function. Quality of life questionnaires have shown improvement with the use of specific surgical techniques.

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Drug-Induced Atrophic Rhinitis

4

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Abbreviations

ANCA	Anti-neutrophil cytoplasmic antibodies
CIMDL	Cocaine-induced midline destructive lesion
GPA	Granulomatosis with polyangiitis
HNE	Human neutrophil elastase
RM	Rhinitis medicamentosa

4.1 Introduction

Drug-induced atrophic rhinitis is a chronic condition characterized by destruction of nasal mucosa and sometimes osteocartilaginous structures, caused by severe chronic inflammation [1].

Many different conditions might be causative of atrophic rhinitis: infective diseases (tuberculosis, syphilis, leprosy, rhinoscleroma); systemic granulomatous diseases involving the upper airways (sarcoidosis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangioitis); non-Hodgkin extranodal lymphomas (Stewart's granuloma), previous sinonasal surgery (empty nose syndrome), and abuse of nasal decongestants or drugs (cocaine) [1–4].

Patients suffering from secondary atrophic rhinitis usually come to the attention of ENT specialists mostly because of chronic nasal obstruction and sensation of

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stuffy nose, which may become a considerable morbidity for them, decreasing their quality of life.

Here are described secondary atrophic rhinitis caused by patient's addiction to nasal vasoconstrictors and cocaine, leading respectively to rhinitis medicamentosa (RM), or rebound rhinitis, and cocaine-induced midline destructive lesions (CIMDLs).

4.2 Rhinitis Medicamentosa

Rhinitis medicamentosa is a drug-induced condition characterized by a nonallergic mucosal inflammation secondary to the overuse of topical decongestants [5].

These drugs mimic the effects of the sympathetic nervous system, stimulating α-adrenoceptors on the vessels of the nasal mucosa in order to cause rapid vasoconstriction.

The nasal mucosal vascular system comprehends capacitance vessels (venous plexus), which expose both α_1 and α_2 adrenoreceptors, and resistance vessels (arterioles), which only expose α_2 adrenoreceptors. Their stimulation provides vasoconstriction of large venous sinusoids, depleting them from blood and reducing nasal edema and rhinorrhea.

Nasal decongestants belong to two main different classes: β-phenylethylamine derivates (pseudoephedrine and phenylephrine), which activate α_1 adrenoreceptors, and also have affinity for β adrenoreceptors; imidazoline derivates (naphazoline, tetryzoline, oxymetazoline, tramazoline, clonazoline, and xylometazoline), which activate α_2 adrenoreceptors on both resistance and capacitance vessels in the nasal mucosa, with a faster and longer effect [3].

These over-the-counter drugs provide rapid relief for patients suffering from nasal congestion typically due to acute or chronic rhinosinusitis. Their effect is however usually short-lasting and it is followed by a rebound congestion which requires new administration, feeding a vicious cycle that eventually damages the nasal mucosa [5].

This kind of secondary rhinitis develops when the abuse of topic decongestants lasts for more than 7–10 days; it affects mainly young and middle-aged adults and its incidence ranges from 1% to 9% of patients referred to otolaryngology clinics [6]. Atrophic rhinitis is the most serious complication of rebound rhinitis [7].

4.2.1 Physiopathology of Rebound Nasal Congestion

There is no clear evidence concerning the mechanism of rebound congestion, only hypothesis. A first assumes that chronic vasoconstriction caused by the prolonged use of topic decongestants leads to hypoxemia and consequent ischemia of the nasal mucosa, which predisposes to inflammation and interstitial edema. Alternatively, reactive hyperemia and edema may also occur because of fatigue of the

overstimulated adrenoreceptors, which became less responsive to both endogenous catecholamines and topic vasoconstrictors, requiring higher doses (tachyphylaxis) [8].

A third hypothesis suggests that an increased parasympathetic activity, which contrapose to the sympathomimetic drugs, may alter vasomotor tone, causing increased vascular permeability and edema [9]. It is also believed that the action of sympathomimetic amines on β adrenoreceptors outlasts the one on the α_1 receptors, causing vasodilation to follow the previous vasoconstriction and resulting therefore in nasal mucosa swelling [10].

Long-lasting use of topic decongestants leads to microscopic changes in the nasal mucosa characterized by destruction of nasal cilia, squamous cell metaplasia, and goblet cell hyperplasia with increased mucus production [11].

4.2.2 Clinical Evaluation

The diagnosis of rhinitis medicamentosa is mostly a clinical diagnosis. Patients usually complain about nasal discomfort, congestion, and stuffiness without rhinorrhea. Severe nasal congestion may lead to oral breathing, dry mouth, and snoring [12]. They usually find temporary relief with topic decongestants, to which they are often addicted.

Clinical evaluation with nasal endoscopy reveals a typically hyperemic nasal mucosa, congested and granular, with areas of increased tissue friability and punctuate bleeding. Pale and edematous appearances have also been noted [13]. As the abuse progresses, the nasal membranes become atrophic and crusty [14].

Biopsy specimens show reduced cilia cell counts, changes in cilia structure, and rupture of basal layer, which predispose to edema, squamous metaplasia, and goblet cells hyperplasia [5].

Biochemical testing or nasal radiologic imaging are not useful to confirm the diagnosis of rhinitis medicamentosa, whereas an accurate assessment of symptoms and history, together with clinical and pathological findings, are conclusive. Differential diagnosis includes allergic rhinitis and other kinds of nonallergic rhinitis but it is important for clinicians to remember that this condition often coexists with other sinonasal pathologies [3].

Turbinate hyperplasia and chronic rhinosinusitis are common findings in RM, while in the most severe cases septal perforation (Fig. 4.1) and atrophic rhinitis may derive from prolonged use of topic vasoconstrictors [15].

4.2.3 Management

A variety of medical and surgical treatments are potentially available to treat patients with rhinitis medicamentosa. Pivotal in healing from this condition is the cessation of the decongestants. Patients must receive counsel that the nasal congestion may temporarily worsen upon discontinuation of topic vasoconstrictors.

Fig. 4.1 Small anterior nasal septum perforation, secondary to decongestants abuse

The use of intranasal corticosteroids has been reported to reduce the symptoms of rebound congestion. Topical fluticasone propionate or budesonide, in fact, activate prostaglandin synthesis, thereby promoting the resolution of the edematous state of the nasal mucosa [16].

The common clinical practice supports the introduction of intranasal steroids while whining from decongestants, to provide relief during the withdrawal period [17].

Saline rinses, short-course oral corticosteroids, antihistamines, and mast cell stabilizing agents may also help in the withdrawal period [10].

Surgical interventions of inferior turbinate reduction are also available to widen the nasal passage, to help patient whining from decongestants [18, 19].

It takes approximately 1 year to recover completely from rhinitis medicamentosa, in case of long-term overuse [20].

4.3 Cocaine-Induced Midline Destructive Lesions

Cocaine is an alkaloid extracted from the leaves of the Erythroxylum coca plant. Its use in rhinological practice began in the nineteenth century, when its uniquely combined anesthetic and vasoconstrictive effect was discovered [21]. In the 1970s, cocaine emerged as a fashionable drug among members of a certain social background, and nowadays it is one of the most trafficked illicit stimulants in both United States and Europe. The European Commission on drug abuse has identified some countries (Spain, UK, Denmark, Ireland, and Italy) with a higher prevalence of use among young adults (15–34 years) [22].

Cocaine stimulates the activity of monoamine neurotransmitters in the CNS and PNS by blocking its presynaptic reuptake, causing euphoria, anorexia, increased alertness, and diminished need for sleep. It also increases dopaminergic activity in the reward system, causing addiction. Additionally, cocaine affects the endothelia;

due to its α-adrenergic stimulation it blocks norepinephrine reuptake at the smooth muscle junction causing vasoconstriction. Furthermore, there is an increased production of endothelin and a decreased release of nitric oxide by endothelial cells, which cause an impaired endothelium relaxation and an augmented central sympathetic activity. Moreover, cocaine predisposes to thrombosis by enhancing platelets aggregation and decreasing fibrinolytic activity [23].

There are two forms of cocaine in the illegal market: base also known as crack, which can be smoked or most commonly snorted, and salt which is administered intravenously or orally. Cocaine metabolism is mainly hepatic, through CYP3A, and its derived metabolites (ecgonine, benzoylecgonine, and ecgonine methyl ester) are excreted with urines in 48–72 h [23].

To maximize the profit, illegal cocaine traffickers use to add "cutting" agents such as phenacetin, caffeine, and lidocaine. The most used one in the last years is levamisole, an anthelmintic agent used in veterinary medicine, which acts synergically with cocaine, potentiating its dopaminergic effect, hence promoting addiction [24]. Unfortunately, it is associated with systemic collateral effects such as agranulocytosis and cutaneous vasculopathy, which may lead to skin necrosis with a pathognomonic pattern of destruction of ear lobes, cheeks, and nasal tip [25, 26].

4.3.1 Clinical Presentation

Snorting cocaine is associated to a well-known kind of drug-induced rhinitis characterized by inflammation of sinonasal mucosa, which slowly leads to progressive destruction of nasal, palatal, and pharyngeal tissues [27].

Once cocaine is snorted, it causes a quick and strong vasoconstriction and anesthesia of nasal mucosa, which is also simultaneously injured by the traumatic effect of cocaine and cutting agent crystals present in the impure admixture sold in the streets. This first reaction is shortly followed by a rebound vasodilation with nasal congestion and hyposmia which induces new administration, hence a chronic reiteration of the mucosal trauma. As repeated, compulsive abuse goes on, the damage produced by the accumulation of chronic ischemic insults leads to the onset of facial pain, epistaxis, nasal crusting and ulceration, hyposmia, and mucopurulent rhinorrhea, since cocaine interacts also with the mucociliary clearance. Chronic ischemia may gradually involve the perichondrium of the nasal septum, creating the quite characteristic septal perforation, found in 4.8% ca of cocaine abusers.

The progressive destruction of nasal septum sometimes spreads centrifugally to lateral nasal walls (middle and superior turbinates, osteomeatal complex) and hard palate, configuring a most extreme condition called cocaine-induced midline destructive lesions (CIMLDs), luckily a rare occurrence despite widespread cocaine abuse by inhalation, even if its true incidence is unknown [28]. In cases of perforation of the hard and sometimes also soft palate, symptoms relative to the oronasal fistula, such as dysphagia and nasal reflux, join the long-standing nasal ones [29] (Fig. 4.2).

Expansion of CIMDL to walls and contents of the orbit has been reported, with the onset of preseptal cellulitis, nasolacrimal duct scarring, diplopia, ocular impaired

Fig. 4.2 Small hard palate perforation and a bigger soft palate perforation, both secondary to cocaine abuse

motility, reduced visual acuity, and optic neuropathy. Rarely severe centrifugal expansion of CIMDL eroded the anterior skull base. External cutaneous ulcers of the nose, upper lip, premaxillary soft tissues, and alar nasal cartilage have also been described, together with typical deformation of nasal pyramid bones, called saddle nose deformity [30] (Fig. 4.3).

Open lesions and necrosis create an ideal environment for anaerobic bacteria, like *Staphylococcus aureus*, that often complicate the situation causing multidrug-resistant infections [27].

4.3.2 Pathogenesis

The pathogenesis of CIMDL in a small subset of predisposed cocaine abusers is poorly understood, but undoubtedly multifactorial.

A pivotal role seems to be played by the ischemic and traumatic effects of cocaine crystals on the nasal mucosa, with the formation of tightly adhering scabs which the patient usually tries to remove, worsening the mucosal damage. Bacterial superinfection is also implicated in the damage process.

What goes unexplained is the rarity of CIMDL among cocaine addicted, given the widespread abuse of cocaine nasal insufflation. What seems to make the difference between patients with a similar use pattern is the personal predisposition to autoimmunity. It has been documented, in fact, the presence of perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) directed primarily against human neutrophil elastase (HNE) in patients suffering from CIMDL. It is possible that bacterial infection with superantigen-producing organisms may lead to ANCA production in predisposed individuals [31]. Most recently ANCA-positive vasculitis from levamisole-tainted cocaine with concomitant CIMDL has been reported, suggesting it could be the substrate to form reactive metabolites capable of triggering an autoimmune response [32]. It does not seem that p-ANCA-HNE auto-antibodies directly participate to the pathogenesis of the disease, yet it is possible that they enhance the local inflammatory response to injury.

Fig. 4.3 Characteristic "saddle nose" deformity with collapse of the left alar cartilage collapse due to preferred use of right nostril for inhalation

In the small subpopulation of abusers that develop CIMDL, apoptosis induced by cocaine in the nasal mucosa has been identified as potential additional key pathogenic factor [33].

4.3.3 Diagnosis

The diagnosis of cocaine-induced rhinitis and CIMDL is challenging, since patients usually do not readily admit their drug abuse. All patients should undergo accurate physical examination of the face, oral cavity, and oropharynx.

Nasal endoscopy usually shows different degrees of mucosal damage, starting from crusts and bleeding spots, necrotic ulcers, and signs of bacterial or mycotic infection. Nasal septal perforation is a common finding (Fig. 4.4); in some cases, there can be a complete or near-total loss of nasal septum, with nasal deformity, saddle nose, and loss of nasal projection [30] (Fig. 4.5).

Few patients who develop CIMDL may show a centrifugal extension of damage, with the loss of inferior, sometimes also middle and superior turbinates and the medial maxillary wall; the hard and soft palate may be involved, with the opening of an oronasal fistula [29].

Blood and urine testing can only detect recent abuse, respectively 48 h and 2–4 days; while hair sample testing has demonstrated to remain positive up to 3 months from latest use [27].

Radiological evaluation is based on CT and MRI imaging. CT scans better assess the grade of bony erosion and its delimitation (Fig. 4.6).

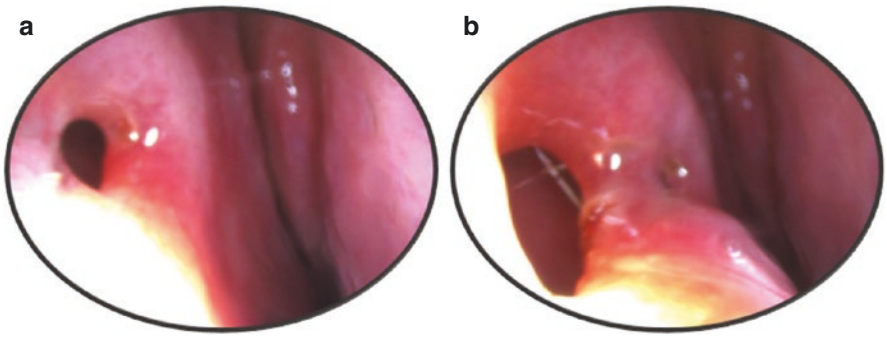

Fig. 4.4 (**a**, **b**) Endoscopic view of nasal septum perforation in ex-cocaine addicted

Fig. 4.5 "Saddle nose" with collapse of left alar cartilage in an elderly cocaine addicted

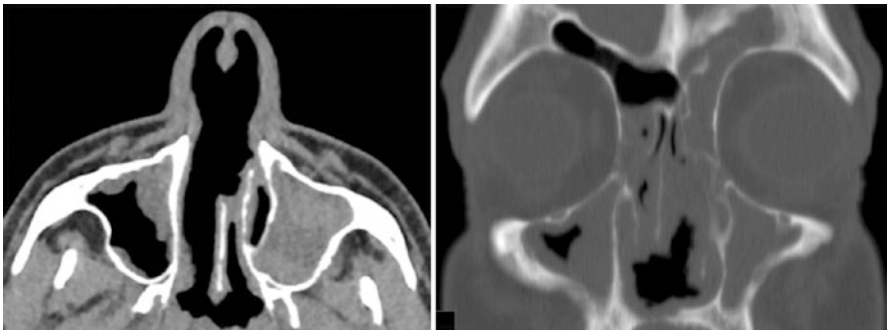

Fig. 4.6 Axial and coronal CT scan show the wide perforation of the nasal septum, associated with the partial resorption of inferior and middle turbinates and sinusitis in a cocaine-addicted patient

MRI imaging with contrast medium provides more information about soft tissue involvement. A common MRI finding in CIMDL patients is diffuse swelling of palatine and pharyngeal tonsils, with small fluid collections embedded in lymphatic tissue [34].

Biopsy specimens must be obtained avoiding necrotic tissues. CIMDL histopathologic features are nonspecific and consist in mixed inflammatory infiltrates, microabscesses in vascular walls, perivenulitis, vascular microthrombotic changes, leukocytoclastic vasculitis, and fibrinoid tissue [30].

Positive anti-neutrophil cytoplasmic antibodies (ANCA) in direct immunofluorescence microscopy are frequent in CIMDL [35]. These auto-antibodies, when tested with antigen-specific solid assay, primarily react with human neutrophil elastase (HLE), displaying a perinuclear staining pattern (p-ANCA) [36].

Since neither clinical evaluation nor histopathological results provide conclusive information, a history of cocaine abuse must be confessed by the patient to confirm the suspect of CIMDL, given the fact that lesions might progress even many years after the complete cessation of the drug abuse [27]. The absence of systemic involvement and the unresponsiveness to treatment via immunosuppressants also corroborates the suspect [37].

4.3.4 Differential Diagnosis

The clinical appearance of CIMDL may closely mimic other diseases. In case patients do not promptly confess drug abuse, infective conditions such as tuberculosis, tertiary syphilis, leprosy, HIV, mucormycosis must be excluded. Epithelial or hematologic neoplasms (Stewart's granuloma also known as lethal midline granuloma) may involve the nose, causing destruction of cartilage, bony and soft tissues. Systemic granulomatous disease may involve the upper respiratory tract, causing granulomatous or necrotizing lesions of the nose (sarcoidosis, granulomatosis with polyangiitis [GPA], microscopic polyarteritis [MPA]).

GPA, also known as Wegener's granulomatosis, represents the main differential diagnosis of CIMDL. It is a systemic illness characterized by necrosis and granulomatous inflammation of the upper and lower airways in conjunction with small vessels vasculitis, together with focal segmental or proliferative glomerulosclerosis [38]. Approximately 50–90% of patients with GPA have nasal signs and symptoms. Vasculitis is most frequently related to the presence of ANCAs, mostly showing a cytoplasmic pattern, directed against proteinase-3 (c-ANCA-PR3) or showing a perinuclear pattern directed against myeloperoxidase (p-ANCA-MPO) [39]. Many histopathologic features are shared between GPA and CIMDL and the differentiation can only be made if the pathognomonic lesions of GPA are found at the biopsy specimen: stromal granulomas with giant cells, microabscesses, and deeply located necrosis. Only 50% of GPA patients display this histological pattern [40]. Two key clinical differences help distinguish GPA from CIMDL: the presence of extranasal involvement in GPA (lung and kidney) and the lack of response to immunosuppressants in CIMDL [24].

4.3.5 Management

The management of cocaine users is a tough clinical challenge. In order to initiate any treatment, the abuse must definitely stop. In some cases, where lesions are mild, discontinuation of the drug may lead to a gradual normalization of the mucosa and the reversal of the pathologic process. In worse cases, the abstention from snorting does not stop the progression of the disease.

Conservative local treatments like careful debridement of necrotic tissue and scabs, regular saline douches, and local or systemic antibiotic therapy are recommended [41]. When considering a surgical approach, a thorough evaluation of the patient must be made, including nasal endoscopy and radiological evaluation. Blood, urine, and hair samples must be tested to make sure the patient has quitted cocaine abuse, since surgical correction of nasal and palatal defects should be postponed until the lesions are stable [24, 42].

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Part III

Diagnosis of Atrophic Rhinitis

5 Empty Nose Syndrome: Clinical Evaluation with Subjective Questionnaires and Psychological Evaluation

Igor Reshetov and Natalia Chuchueva

5.1 Introduction

Subjective emotional and health state of patient should be considered as one of the most important outcomes of any treatment or investigation. World Health Organization (WHO) outlines that the assessment of health and the health care effectiveness must include not only an appraisal of changes in the frequency and severity of diseases but also an estimation of well-being. This can be assessed by measuring the changing in the quality of life (QoL) related to health problem [1]. Thus, in order to control the efficiency of treatment approach, it is very important to have a validated measurement unit for the assessment of subjective health condition. Especially, it should be taken into consideration in case of disease that strongly influences every day activity of patients.

Both primary and secondary, along with iatrogenic, atrophic rhinitis have a significant unfavorable impact on every day patients' life and can cause dramatic reduction in quality of life [2]. Particularly, an empty nose syndrome (ENS) places a huge psychological burden on the individuals suffering from this pathology [3]. It can cause clinically important secondary depression [3] that has shown to be of a great significance [4]. So, improvement of the QoL that can be reported by patient itself should be the main aim of the treatment of atrophic rhinitis and empty nose syndrome.

According to one of the definitions from WHO, quality of life includes psychological and both social and physical functioning. It associates positive aspects of well-being as well as negative aspects of disease [1]. Health-related quality of life

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(HRQL) is a part of QoL that is influenced by health. It evaluates the impact of an illness and its treatment on functioning, as perceived by the patient [5]. HRQL can be assessed by questionnaires. They provide a standardized method of the patients' physical symptoms verification and the functional and psychosocial consequences of the disease and its treatment [5]. Clinical practitioners widely use HRQL measurement methods both in the clinical and scientific practice along with other diagnostic techniques [6–8]. Questionnaires can be used to identify individuals with various conditions as well as to assess the effectiveness of the treatment [9].

Many questionnaires have been developed to assess the impact of rhinitis and rhinosinusitis on individual patients and to monitor the response to treatment [10]. But none of them was proved to be correct in the assessment of clinical and psychological burden of an empty nose syndrome.

5.2 Clinical Evaluation with Subjective Questionnaire

5.2.1 SNOT-25 (ENS Modification)

The earliest mention of SNOT-25 in modification for ENS assessment was done by Chhabra and Houser [11]. They modified it from existing SNOT-20 questionnaire [12] and specially devoted it for patients with empty nose syndrome. Five additional items were included into the newly created SNOT-25: dryness, difficulty with nasal breathing, suffocation, nose is too open, and nasal crusting [11].

The validity of SNOT-25 in ENS modification was evaluated by Jiang and coauthors and the Cronbach α value of 0.90 demonstrated a high internal consistency and a level necessary for clinical application [13]. Authors reported that the study results suggested a satisfactory test–retest reliability and concluded that SNOT-25 is a legitimate tool that can be routinely used in clinical daily practice [13]. But it should be mentioned that sensitivity and specificity of the test were not provided in that study.

SNOT-25 in ENS modification was successfully used as a measurement of treatment effectiveness in several studies [14–21] and showed favorable results considering improvement reporting after the treatment. Hong and coauthors showed that a smaller inferior turbinate volume is significantly associated with specific SNOT-25 items in patients with empty nose syndrome [22].

It should be mentioned that there might be terminology confusion between different SNOT-25 questionnaires. Besides the SNOT-25 in Chhabra and Houser modification that was designed for empty nose syndrome assessment, there were two more modifications that were called SNOT-25 as well. Publication from *The Laryngoscope*, dated 2006, was using another SNOT-25 modification done for the assessment of nasal symptoms of Wegener's granulomatosis and was designed on the basis of SNOT-22 adding additional three questions relevant to Wegener's granulomatosis (nasal crusting, bleeding, and external nasal deformity) [23]. Another one was presented in 2019 by Tait and coauthors and was modified on the basis of SNOT-22 to better assess severity of rhinosinusitis [24]. SNOT-25 in ENS modification is presented in Table 5.1.

Table 5.1 SNOT-25 in ENS modification questionnaire [11]

	Scoring range (0–5)					
SNOT-25 symptoms	0[a]	1	2	3	4	5[b]
Need to blow nose						
Sneezing						
Runny nose						
Cough						
Postnasal discharge Thick nasal discharge						
Ear fullness						
Dizziness						
Ear pain						
Facial pain/pressure						
Difficulty falling asleep						
Waking up at night						
Lack of good night's sleep						
Waking up tired						
Fatigue						
Reduced productivity						
Reduced concentration						
Frustration/restlessness/irritability						
Sadness						
Embarrassment						
Dryness						
Difficulty with nasal breathing						
Suffocation						
Nose is too open						
Nasal crusting						

[a]No symptoms
[b]Severe symptoms

5.2.2 ENS6Q

Despite SNOT-25 in ENS modification was validated in one study with high internal consistency [13], the specificity and sensitivity of this test have never been assessed. Moreover, final SNOT-25 score for patients with empty nose syndrome was not measured and stated, and the terminology confusion mentioned above should be kept in mind.

So, all these rationales lead to the development of ENS6Q. This questionnaire was specially designed and dedicated for measurement of QoL in ENS patients and firstly proposed in 2016 by the international group of authors [25]. According to the authors, this tool can aid in making the diagnosis of empty nose syndrome and provide a quantifiable outcome measure for QoL in ENS patients. Authors reported that they considered four of the questions from the SNOT-25 to be valid for use in the ENS6Q. They specified quality of nasal breathing and/or nasal congestion into the "sense of diminished airflow (cannot feel air flowing through your nose)." Finally,

Table 5.2 ENS6Q questionnaire [25]

Symptom	Scoring range					
	No problem/not applicable	Very mild	Mild	Moderate	Severe	Extremely severe
	0	1	2	3	4	5
Dryness						
Sense of diminished nasal airflow (cannot feel air flowing through your nose)						
Suffocation						
Nose feels too open						
Nasal crusting						
Nasal burning						

they added the question on "nasal burning," given that it is a common symptom stated by ENS patients. The ENS6Q questionnaire is shown in Table 5.2.

In the same study [25], ENS6Q was validated on three cohorts of patients. One cohort consisted of patients with empty nose syndrome ($n = 15$), second one with chronic rhinosinusitis without polyps ($n = 30$), and third group was healthy controls ($n = 30$). Participants completed two independent rounds of both the SNOT-22 and ENS6Q questionnaires. As a result of the study, the Cronbach α value of 0.93 for the ENS6Q demonstrated high internal consistency. Specificity and sensitivity for total ENS6Q score for ENS diagnosis were 96.6% and 86.7%, respectively. Whereas predictive values of SNOT-22 for ENS diagnosis were 62.1% and 66.7%. Authors established a diagnostic score cutoff within the ENS6Q of 10.5. So, a score of 10.5 of 30 on the ENS6Q can reliably predict ENS. Authors concluded that ENS6Q can be a valid disease-specific questionnaire in the evaluation and diagnosis of ENS, with consistent test–retest internal reliability and consistency.

Later, Thamboo and coauthors used ENS6Q questionnaire to validate cotton test. They revealed that seven-point change after treatment should be achieved to demonstrate a minimal clinically important difference [26]. Later, ENS6Q score system was applied in the studies either to establish ENS patients or to assess effect of the treatment [27–33].

5.2.3 Other Questionnaires That Were Applied for Empty Nose Syndrome Assessment

Questionnaires that initially have been used for rhinosinusitis and rhinitis were used for atrophic rhinitis as well. Li and coauthors established that patients with ENS had significantly elevated SNOT-22 (58.22 ± 15.85) and NOSE scores (69.35 ± 17.1) [27]. In the study conducted by Tam and coauthors, the preoperative summation score on SNOT-22 was 39.25 ± 21.44 [34]. In the study of Borchard, SNOT-22

Table 5.3 Scores in different rhinitis questionnaires got for patients with atrophic rhinitis

Author/year of publication	Sample size/ diagnosis	Type of questionnaire with a mean score available from publications		
		SNOT-22	NOSE	RhinoQoL
Bastier/2013 [36]	5/ENS	–	90	18.7; 30; 62.5
Tam/2014 [34]	18/ENS	39.25 ± 21.44	–	–
Li/2018 [27]	27/ENS	58.22 ± 15.85	69.35 ± 17.1	–
Borchard/2019 [29]	14/ENS	50.03 ± 15.02	–	–
Malik/2019 [32]	27/ENS	58.2 ± 15.9	69.4 ± 17.1	–

score was 50.03 ± 15.02 in patients with empty nose syndrome [29]. In the study of Malik, SNOT-22 average score was 58.2 ± 15.9 for ENS patients and NOSE score 69.4 ± 17.1 [32]. SNOT-22 score for a patient with ENS was 23 in the study of Tracy and coauthors [35]. In the study of Bastier, NOSE score in patients with ENS was 90, RhinoQoL frequency, bothersome, and impact were 18.7, 30, and 62.5, respectively [36]. All the scores are presented in Table 5.3.

Empty Nose Syndrome International Association (ENSIA) proposed greatly enlarged questionnaire adding 30 items to SNOT-25 in Houser modification. It can be found on several internet sources [37]. First block includes 25 questions from SNOT-25 in Houser modification. Questions 26–37,40,54 covers breathing-related component of ENS:

> *"26) Nasal obstruction; 27) Nasal emptiness; 28) Excessive airflow; 29) Decreased nasal resistance; 30) Shortness of breath; 31) Difficulty to inflate lungs; 32) Difficulty drawing a full breath; 33) Disturbed/disorganized airflow; 34) Decreased sense of nasal airflow; 35) Weakened airflow; 36) Tight, asthma-like breathing; 37) Use of accessory muscles to facilitate breathing; 40) Rapid breathing; 54) Persistence of symptoms when mouth breathing."*

Other rhinological symptoms are listed as questions 41–47:

> *"41) Reduced sense of smell; 42) Lack of mucus; 43) Nasal burning/pain; 44) Nasal bleeding; 45) Nasal inflammation; 46) Impaired nasal drainage; 47) Difficulty removing thick mucus/clear nose."*

Secondary physical symptoms, cognitive and functional limitations presented as:

> *"48) Dry eyes; 49) Headache; 50) Increased heart rate; 51) Impaired concentration from breathing difficulties; 55) General disability."*

Here you can get a general idea of this greatly expanded questionnaire. Detailed description of every inventory item can be found in the original document [37]. Unfortunately, to our best knowledge, this questionnaire was neither used in scientific investigations nor validated.

5.3 Psychological Evaluation (Mental Health Questionnaires)

Patients with all types of atrophic rhinitis suffer from greatly impaired daily activity, dramatically reduced quality of life and even secondary depression. The most well-defined psychological impairment was described for empty nose syndrome. Comorbid psychiatric illness is highly prevalent in this type of patient population [38]. The study of Kim and coauthors demonstrated that the degree and severity of depression in ENS patients is higher than that in patients with chronic rhinosinusitis and even allergic rhinitis [39]. Patients with empty nose syndrome may experience anxiety and depression that may even lead to suicide attempts [3, 40]. In 2001, Moore and Kern reported about high prevalence of depression among patients with atrophic rhinitis: among 242 examined patients ,125 were diagnosed with depression on the basis of Multiphasic Personality Inventory and/or consultation with a psychiatrist [41]. Jiang and coauthors reported about five predominant symptoms according to SNOT-25 that were reported by patients with empty nose syndrome. Two of them were nasal symptoms ("dryness" and "nose is too open") and three psycho-emotional symptoms ("fatigue," "reduced concentration," and "sadness") [13]. According to another study, the most bothersome symptoms for patients with atrophic rhinitis were fatigue, facial pain or pressure, and lack of a good night's sleep [42]. Most of these symptoms are related to psycho-emotional sphere.

Beck Depression Inventory-II (BDI-II) [43] and Beck Anxiety Index (BAI) [44] were mostly used in the abovementioned studies. Both these depression inventories were proved to have high internal consistency [45, 46].

The BDI-II [43] was proposed by Beck as an advanced version of his first inventory [44]. Nowadays it is one of the most frequently used questionnaires for the assessment of severity of depression. It includes 21 questions:

> *"1) Sadness; 2) Pessimism; 3) Past failure; 4) Loss of pleasure; 5) Guilty feelings; 6) Punishment feelings; 7) Self-dislike; 8) Self-criticalness; 9) Suicidal thoughts or wishes; 10) Crying; 11) Agitation; 12) Loss of interest; 13) Indecisiveness; 14) Worthlessness; 15) Loss of energy; 16) Changes in sleeping pattern; 17) Irritability; 18) Changes in appetite; 19) Concentration difficulty; 20) Tiredness or fatigue; 21) Loss of interest in sex."*

Every item is followed by four response options. Respondent should choose one statement that best describes the way he or she has been feeling during the past 2 weeks. A total BDI-II score that falls within range 14–19 indicates mild depression and 20–28 indicates moderate depression. The mean score above 28 reveals severe depression [43].

The BAI was firstly introduced in 1988 [44]. The self-reported inventory consists of 21 items for anxiety measurement. The respondent should rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 (not at all) to 3 (I could barely stand it) [44]. BAI questions with the scoring range are presented in Table 5.4. Total score can range from 0 to 63. Total BAI score of 0–7 indicates normal, 8–15 indicates mild anxiety, 16–25 indicates moderate anxiety, and 26–63 indicates severe anxiety [47]. Available mean ranges

Table 5.4 Beck Anxiety Index questionnaire

	Scoring range (0–3)			
Symptom	0	1	2	3
Numbness or tingling				
Feeling hot				
Wobbliness in legs				
Unable to relax				
Fear of the worst happening				
Dizzy or lightheaded				
Heart pounding or racing				
Unsteady				
Terrified				
Nervous				
Feeling of choking				
Hands trembling				
Shaky				
Fear of losing control				
Scared				
Indigestion or discomfort in abdomen				
Faint				
Face flushed				
Sweating (not due to heat)				

Table 5.5 Mean score of mental health questionnaires for ENS patients

		Mean psychological scores for ENS patients[a]		
Author/year of publication	Sample size/diagnosis	BDI	BDI-II	BAI
Ta-Jen Lee/2016 [40]	20/ENS	–	24.4	19.0
Ta-Jen Lee/2018 [48]	30/ENS	–	22.6	13.8
Chia-Hsiang Fu/2019 [49]	19/ENS	–	15.0	21.0
Chien-Chia Huang/2019	68/ENS		19.3	17.7
Chang Hoi Kim/2019 [39]	24/ENS	12.6	–	

[a]Standard deviation is not present in the table since it was not provided by all authors

of BDI-II and BAI for ENS patients are presented in Table 5.5. PHQ-9 and PHQ-2 can be used as well, along with precise mental health examination. In the study of Borchard, PHQ-9 depression score was 11.6 at baseline in patients with ENS [29].

5.4 Conclusion

According to the literature, SNOT-25 in ENS modification and ENS6Q questionnaires are considered to be the most relevant and specified for ENS patients. Both can be used in clinical practice. SNOT-25 might be more relevant for atrophic rhinitis with spared anatomical structures since it has rhinitis-related questions. ENS6Q

questionnaire is strongly dedicated for empty nose syndrome. But in any way, it is better to come into consensus what questionnaire to use as to make easier literature data analysis. It might be of great value to report both SNOT-25 in ENS modification and ENS6Q in the researches. Even considering high validity of these questionnaires reported in the studies, they should be auxiliary to exhaustive history and physical examination along with depression and anxiety evaluation.

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The Role of Nasal Cytology in the Diagnosis of Atrophic Rhinitis

6

Matteo Gelardi and Michele Cassano

6.1 Introduction

Atrophic rhinitis (AR) is a poorly understood chronic disease process characterized by atrophy of the nasal mucosa, formation of nasal crusts, and a characteristic foul smell [1, 2]. It shows a female predominance (5.6:1; other sources state 6:1.5, female/male), and it is endemic in subtropical and temperate climate zones, where its incidence ranges from 0.3 to 1% of the population [3–5]. Diagnosis is based on history and exclusion of other pathological entities, based on diagnostic criteria [6]. Although known since ancient times and first described in the medical literature by Fraenkel in 1876, the underlying aetiology and management of this disease remain a contentious issue in the medical literature. Partly to blame is the use of several terminologies to refer to atrophic rhinitis, including atrophic rhinosinusitis, rhinitis sicca, rhinitis fetida and ozaena [7, 8]. Regardless of the term, atrophic rhinitis is a progressive disease in which its management, whether medical or surgical, largely serves to mitigate but not to arrest the process.

AR is characterized by a sclerotic change in the mucous membrane of the nose and by abnormal patency of the nasal passage due to atrophic changes in the mucosa and underlying bone [9]. The disease is also characterized by thick, viscous secretions that, when dried, can cause a peculiar foul smell. The smell makes the patient rejected in society. Additional symptoms include a sensation of dryness in the nose, nasal obstruction, episodic epistaxis and, in some cases, perforation of the nasal septum. Atrophic changes in turbinates and nasal bones produce a large nasal cavity and atrophy of the olfactory nerve causes anosmia. Miles and Taylor [10] have extensively studied the pathology of AR. They found that chronic rhinitis causes endarteritis and periarteritis of the terminal arterioles, leading to atrophic pathology

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with infiltration of chronic inflammatory cells, mainly lymphocytes, and fibrosis in about 23.5% of AR cases. However, the aetiology of AR remains ambiguous; many theories are postulated in the explanation. The factors that may cause the genesis of AR are *Coccobacillus*, *Bacillus mucosus*, *Diphtheroid bacillus*, *Klebsiella ozaenae*, chronic infection of the sinuses, autoimmunity, hormonal imbalance, malnutrition, heredity and iron deficiency anaemia [11, 12].

Although the underlying aetiology of atrophic rhinitis has not been elucidated yet, a refinement of the disease process into primary and secondary forms was first made by Ruskin in 1932. Primary atrophic rhinitis is principally evident in developing countries in the subtropical and temperate climate zones, it is also closely related to infectious pathogens.

Secondary atrophic rhinitis is the most prevalent form in the developed countries. It is often secondary to inadequate and demolitive surgical treatments.

On physical examination, the turbinates appear atrophied and the nasal cavities abnormally wide. Abundant exudate forms crusts covering part of the nasal mucosa, where crust-free areas appear dry and opaque.

6.2 Histocytological Aspects of the Nasal Mucosa

Microscopically, the nasal mucosa consists of an epithelium resting on a thin basal membrane that separates it from the *tunica propria* [13]. The pseudostratified columnar epithelium (Fig. 6.1) is composed of ciliated and non-ciliated columnar cells. The latter are also called brush border or striated cells, muciparous goblet cells and basal cells. All these cells are closely interconnected through desmoidal and hemidesmoidal junction systems. Lymphocytes and polymorphonucleates can sometimes be observed in the intercellular spaces.

Although the epithelial mucosa is generally considered to be a mere physical barrier between the organism and irritating agents (chemical, physical, bacterial and viral agents), it is, in fact, metabolically active. For instance, in immune inflammatory reactions, it plays an important role in regulating host response, producing a wide variety of inhibitors.

The ciliated cell is the most differentiated and the most numerous cell type, accounting for about 80% of the cells making up the nasal mucosa.

The ratio between ciliated and non-ciliated cells is normally 5:1 (Fig. 6.2a, b), and it increases proceeding distally toward the lower airways where it peaks at 100–200:1.

Ciliated cells are elongated polygons, 15–20 μ high, with nuclei located at various heights above the basal membrane, giving the epithelial mucosa its typical pluriserrated appearance under microscopy. The top surface is composed of about 100–250 cilia (each 10–15 μ long and 0.2 μ across) and about 300 microvilli.

The respiratory epithelium is separated from the *tunica propria* by the basal membrane, a thin hyaline membrane (0.2 μ thick) perforated by openings through

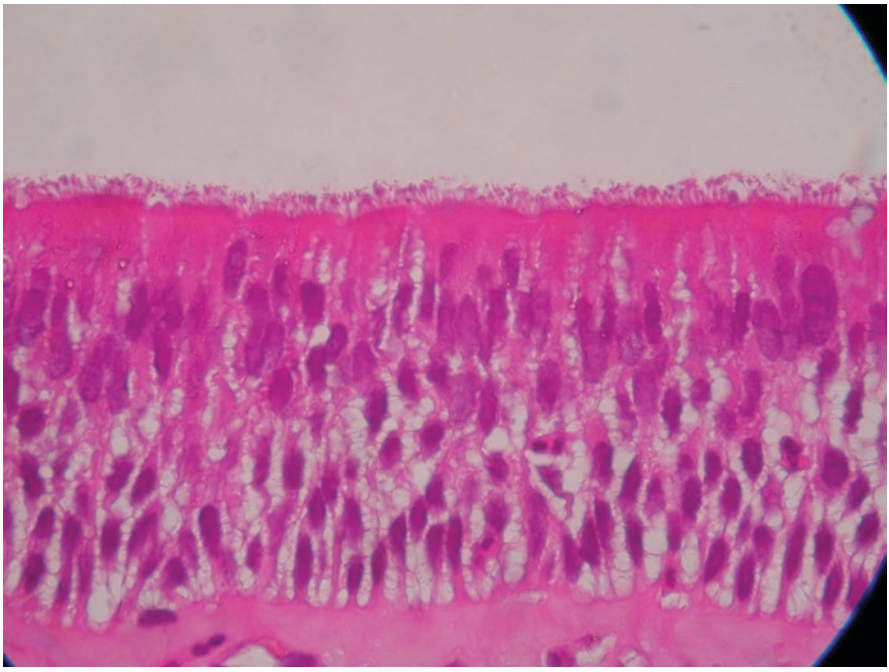

Fig. 6.1 Nasal mucosa: Ciliated pseudostratified epithelium. (Histological preparation)

which leukocytes migrate toward the epithelial surface; it is highly resistant and strongly adherent to the epithelial cells.

The *tunica propria*, or stroma or chorion, is composed of fibroelastic connective tissue on which the epithelium rests and extends to the periosteum and perichondrium.

The stroma has three layers:

– the subepithelial or lymphoid layer
– the intermediate or glandular layer
– the deep area or venous-pseudocavernous zone.

The subepithelial layer lying beneath the basal membrane is relatively lax and rich in lymphocytes, hence the term lymphoid, which are often arranged in nodules (nasal-associated lymphoid tissue [NALT]) [14], especially in the posterior portion of the nasal cavity.

The intermediate layer is rich in glandular bodies. Their secretion has an anti-infectious action owing to the presence of lysozyme and immunoglobulins (primarily IgA class) [15]. These submucosal glands, some of which are serous, others mucus or mixed, have a tubuloacinar structure similar to the salivary glands.

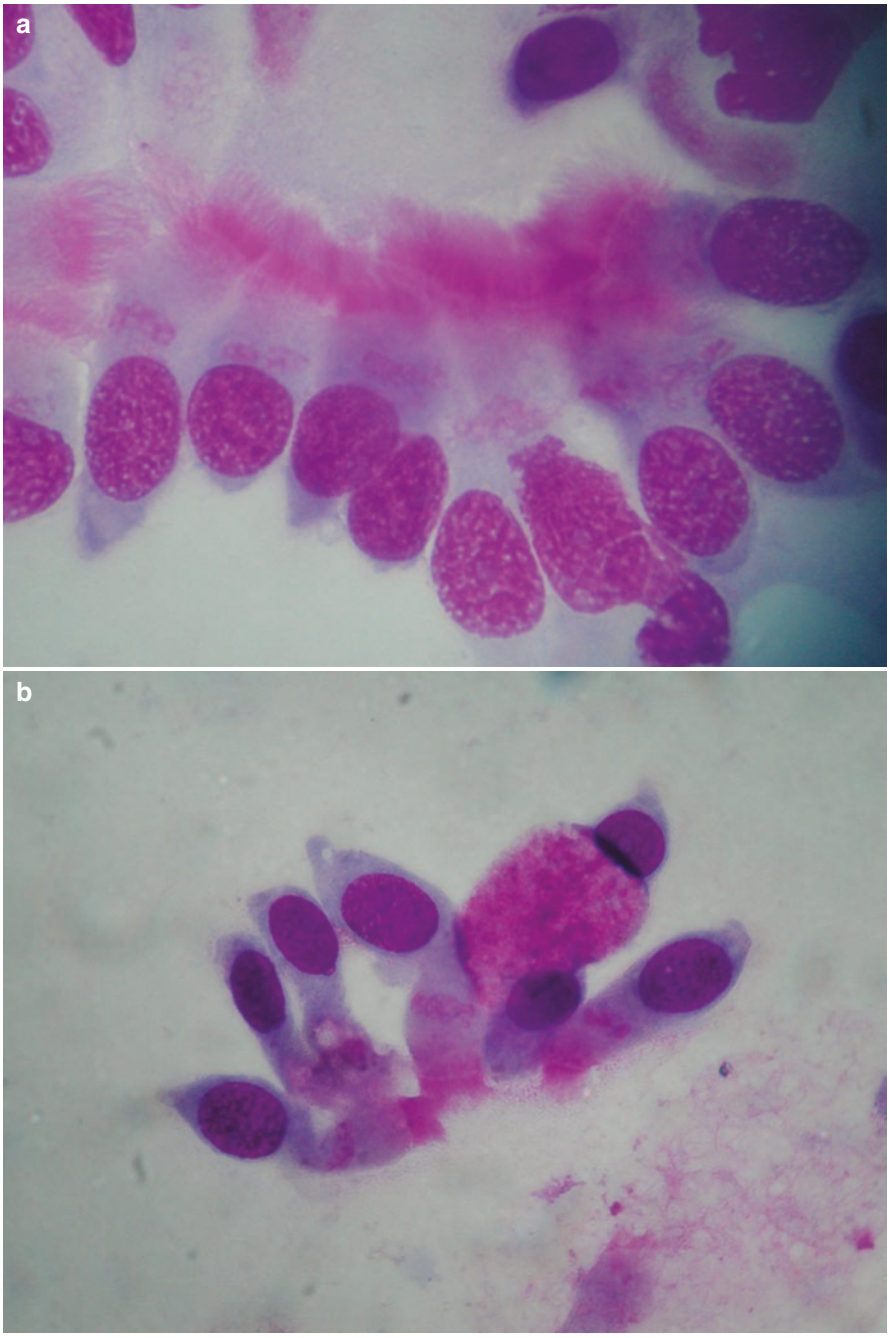

Fig. 6.2 (**a**) Normal cytology. Numerous ciliated cells with prominent ciliary apparatus (MGG staining; 1000× magnification); (**b**) Ciliate cells and muciparous cell in characteristic ratio of 5 ciliated to 1 goblet cell (MGG staining; 1000× magnification)

The deeper layer has a vascular architecture that can be appreciated particularly in the inferior turbinate, the free margin of the middle turbinate and the middle portion of the septum. The arteries run nearly straight up from the deeper to the upper areas of the mucosa where they form a dense subepithelial capillary network, whence thin-walled venules branch out and join to form the cortical structure of the erectile body. This characteristic structure of the vascular system is typical of the nasal mucosa but is absent in the sinuses.

6.2.1 Histopathological Studies

The histological changes that characterize atrophic rhinitis have been described for some time now [16], and they consist of:

- Metaplasia of respiratory epithelium to stratified squamous epithelium even with keratinization.
- Glandular atrophy affecting both the mucous and serous types; the mucous glands shows early atrophy.
- Inflammatory cellular infiltrations of the *tunica propria* mainly by lymphocytes and plasma cells.
- Excessive fibrosis of the *tunica propria* in advanced cases, in some cases hyalinosis of the *tunica propria*. Pigment masses can be encountered in the tunica propria, proved to be haemosiderin pigment by Prussian blue reaction.
- The main picture concerning the blood vessels changes is the marked endarteritis obliterans together with thickening of the media.
- In some of the cases, the *tunica propria* shows oedema and polypoid formations.

6.2.2 Cytological Alterations by Nasal Cytology Study

Nasal cytology covers an important area of research in rhinosinus pathology, mainly concerning vasomotor rhinitis (VMR) and infective nasal disease, since it is a valid method in the differential diagnosis of allergic and non-allergic, bacterial and viral diseases. This is a well-known method, considering that Gollash [17] in 1889 observed that the presence of eosinophils in the nasal secretion of patient with bronchial asthma was an important element in the pathogenesis of the disease [18–20]. Many factors have contributed to increase the interest about this diagnostic procedure, including the simplicity of nasal sampling, the scarce invasiveness of the techniques and the repeatability of the rhinological exams, which is often necessary in the follow-up visits to monitor the efficacy of medical-surgical treatments [21]. The simplicity of the methods, the non-invasive safety, the cost-effectiveness and the possibility of performing the exams in the clinical office setting, makes nasal cytology applicable also in paediatric subjects [22].

6.3 Cytological Techniques

The cytological method consists of the following:

– Sample collection (also known as sampling).
– Processing (which involves fixing and staining).
– Microscopic observation.

Cytological sampling consists of harvesting the superficial cells of the nasal mucosa, which can be performed by using a sterile tampon (e.g., the same used for pharyngeal sampling), or a small plastic curette (Nasal Scraping®, EP Medica, Italy), or by scraping the nasal mucosa. In retrieving samples from the nasal mucosa, the nasal tampon must be twisted with moderate pressure to remove a large quantity of mucosal cells, corresponding to the medial portion of the inferior turbinate, notably the area where there is an equal ratio of ciliated cells and goblet muciparous cells (ratio of 1/4 in favour of the ciliated cells). Usually, in the case of young patients, a nasal tampon is preferred instead of scraping the surface of the mucosa, since it is quicker with less inconvenience for the patient; furthermore, an abundant quantity and quality of cell samples are collected. The sampling is always carried out with careful visual attention, with anterior rhinoscopy using a nasal speculum and good illumination. The method is not invasive, so it does not require any anaesthesia. After the samples are collected on the nasal tampon, they are spread on a microscope cover slide, hence they are fixed and stained with May-Grunwald–Giemsa. This stain is usually used since it stains all the cytological components present in the nasal mucosa, including the inflammatory cells (such as neutrophils, eosinophils, lymphocytes and mast cells), bacteria and mycotic spores. The smear is observed under a common light microscope equipped with a 1000× magnification. For the rhinocytogram, the procedure is to read as many fields as possible on the entire surface of the cover slide, in order to understand which cellular elements are involved for the diagnosis (neutrophils, eosinophils, lymphocytes and mast cells, bacteria and spores) and evaluating the percentage of the cell types in at least 50 microscopic fields [13].

As previously described, the nasal mucosa is classically composed of four cell types (ciliated, muciparous, striated and basal) and some rare neutrophils. Therefore, finding other cell types is an index of probable disease.

In AR, after an initial cytological picture characterized by a gobet cell metaplasia (Fig. 6.3), which is typical of a proliferative non-differentiated response and an exclusive prerogative of the ciliated epithelium, it moves on to diffuse squamous metaplasia, (Fig. 6.4a, b) in which there is a reduction of seromucosal glands and gobet cells as described by recent studies [23].

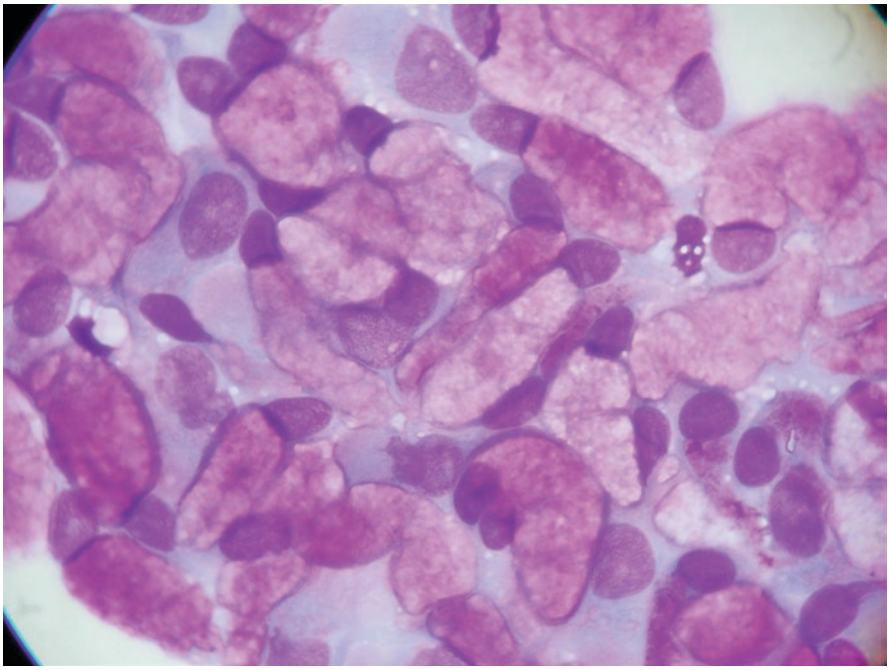

Fig. 6.3 Muciparous metaplasia (MGG staining; 1000× magnification)

In addition, the reduction/absence of mucociliary clearance represents a risk factor in the formation of biofilm [24], (Fig. 6.5) which is responsible of relapsed nasal infections.

On the basis of all said above, it can be stated that both nasal histology and cytology show the same mucosal alterations of the nasal cavities in AR, where the most evident aspect is the complete rearrangement of the respiratory epithelium, mainly dominated by a non-differentiated flat epithelium.

Most of the time, it is an irreversible damage that forces patients to undergo, for a long time, pharmacological treatments (local and general antibiotics) [25], supplements (vitamins A and E) [26] and to use medical devices (nasal douches with physiological solutions associated with hyaluronic acid treatments) [27, 28], in order to improve the trophism of nasal mucosa, reduce scabs formation and forestall superinfections.

In the context of prevention, the role of the surgeon is certainly fundamental in safeguarding the anatomical–functional integrity of nasal mucosa, avoiding all the surgical procedures which could lead to those pathological conditions nowadays enclosed under the term “empty nose”.

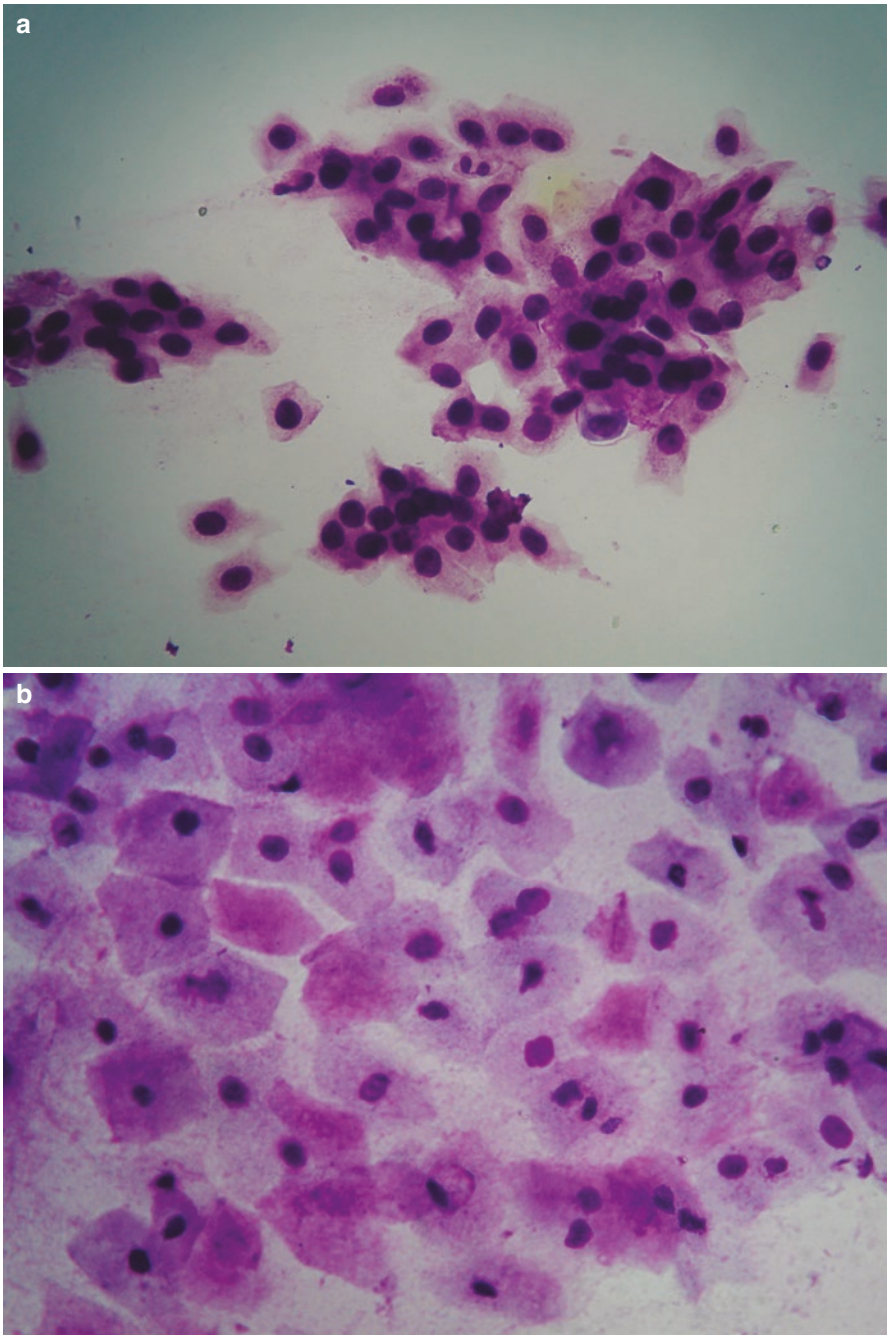

Fig. 6.4 (**a**) Atrophic rhinitis (MGG staining; 400× magnification); (**b**) Atrophic rhinitis (MGG; 1000× magnification)

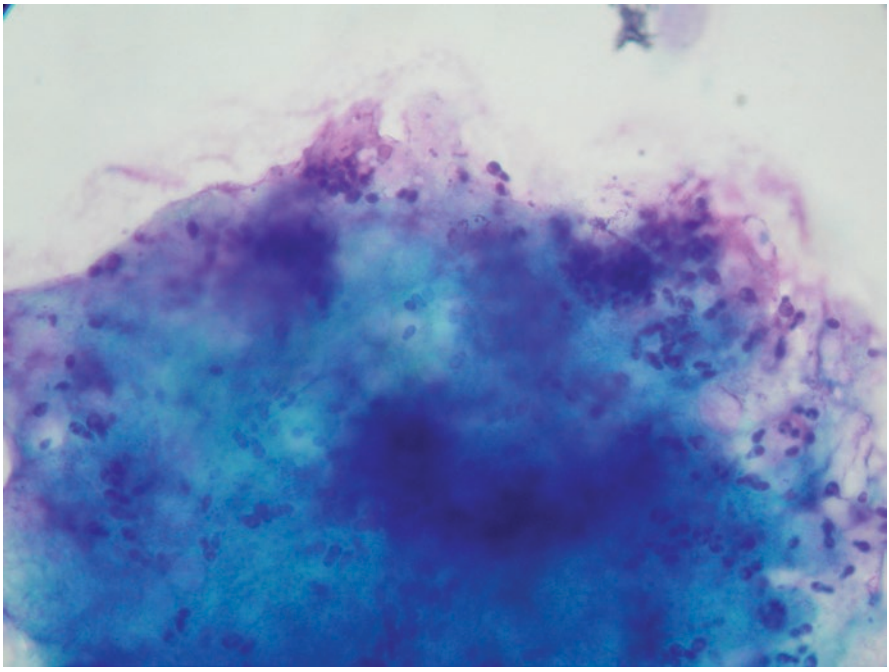

Fig. 6.5 Biofilm. Visible colonies of bacteria embedded in a brightly coloured cyan matrix. (MGG staining; 1000× magnification)

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The Role of Rhinomanometry and Nasal Airflow Evaluation in the Diagnosis of Atrophic Rhinitis

7

Francesco Maria Passali, Giancarlo Ottaviano, Giulio Cesare Passali, and Stefano Di Girolamo

7.1 Introduction

It is a common notion that breathing through the nose is the only physiological form of breathing as it is proved by this irreplaceable function at the time of birth and the numerous anatomical, functional, and psycho-behavioral alterations induced by the breathing through the mouth.

However, this natural and apparently simple way of breathing presupposes the existence of fine mechanisms and functions of cleaning and heating of the air breathed in, with which the nasal mucosa is endowed. It is, in fact, the task of the nose to change the physical characteristics (temperature and humidity) of the air, making them suitable for the gaseous exchanges at pulmonary level and providing in addition a cleaning function from pollution, allergens, viruses, and bacteria.

The morphological integrity of the osteocartilaginous structures, as well as of the mucosa and epithelium that cover them, is an indispensable prerequisite to carry out a physiological nasal breathing and for the ventilation of the paranasal cavities.

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In same way, a correct evaluation of the clinical symptoms cannot be separated from the analysis of the underlying pathophysiological mechanisms and the morphological alterations that determine them.

Nasal breathing takes place under conditions of resistance over 50% higher than that of oropharyngeal airway. In the course of calm breathing, the volume of the air, which crosses the nasal valve at the speed of 2–3 m/s, is distributed in three main streams: the main one passes along the middle meatus, another accounting for 5–10% reaches the olfactory fissure following an almost vertical route, and the third one laps the nasal floor. To the laminar flows crossing the three meati, microturbulences are added which are more accentuated behind the nasal valve: they guarantee an adequate mixing and increase the contact between the air and the mucosa allowing the exchanges of heat and humidity, as well as the function of cleaning, more efficient.

The proper nasal valve, although differently identified by various authors starting from the first definition of Mink [1], corresponds to the fissure delimited by the alar, triangular, and septal cartilages; it is responsible for one-third of total nasal resistances [2], it responds to mechanical stresses, and it is modulated by voluntary muscles. Two-thirds of nasal resistances are due to the turbinates valve [3], i.e., the neurovascular control of the turbinates cavernous tissue [4].

This is why, on the whole, it is more correct to speak about the "nasal valve area" (Fig. 7.1) or "flow-limiting segment" [5] where cartilages, muscles, mucosa, and epithelium all together contribute to supply the lower respiratory apparatus with quantitatively and qualitatively adequate air for the pulmonary gaseous exchanges. Thanks to the nasal valve area, the airflow through the nasal cavities follows the Poiseuille's law with a laminar flow and microturbulences around the unevenness of the nasal fossae walls. In this way, the contact of the air with the mucosa is increased, the ideal air temperature and humidity are reached, and the ciliated epithelium provides the cleaning from pollution, allergens, viruses, and bacteria.

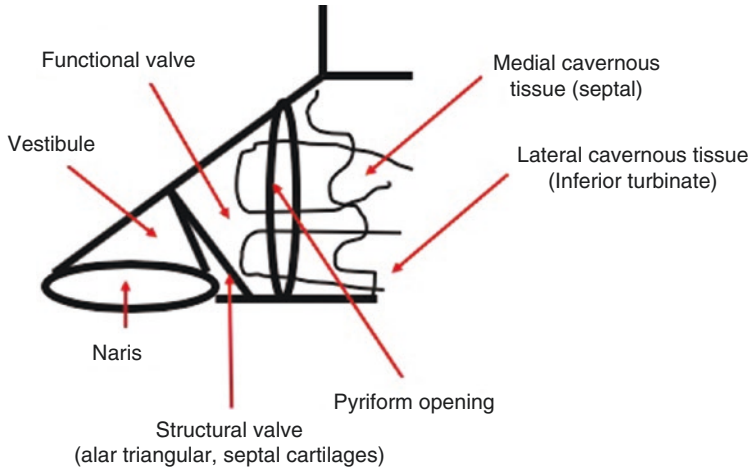

Fig. 7.1 Schematic view of the "nasal valve area"

Fig. 7.2 Microcorrosion cast of an arteriovenous anastomosis

In fact, the conditioning of the air is guaranteed by the presence of the cavernous tissue and the arterious-venous shunts of the turbinates microcirculation. The breathing in of cold air stimulates, in a reflex way, the opening of the arterious-venous shunts, increasing the exchanges of heat at the air–mucus interface, while, on the contrary, breathing in of hot air leads to the constriction of afferent arterioles. The degree of repletion of the cavernous spaces, on the other hand, is modulated by the conditions of environmental humidity: if the air is dry, the water transudes from the turgid sinusoids toward the mucosa surface as a result of osmotic phenomena.

The three-dimensional aspect of the vascular architecture of the nasal mucosa was studied in human fetuses using the microcorrosion method followed by scanning electron microscopical observation of casts of the vascular networks in both the septum and the lateral wall of the nose [6]. Thanks to this technique, it was possible to identify three vascular layers: the most superficial located in the subepithelium; the intermediate layer and the deepest one, most probably composed of vessels supplying the perichondrium and periosteum. It was also possible to observe the arterious-venous anastomosis and to differentiate veins (which usually have an irregular course) and arteries (with a straight course) (Fig. 7.2).

The filtering of the more voluminous particles (>50 μ) in the air breathed in is due to the vibrissae originating from the skin of the nasal vestibule: they protrude into the lumen of the nostril orifice and are particularly sensitive to even the slightest deformation, but not to powerful stresses such as sneeze. The respiratory epithelium with ciliated cells and goblet cells is entrusted with the mucociliary transport whose efficiency is linked to the integrity of cilia and the physical properties of nasal secretion.

Worth of mention, among all these complex functions and the neurovegetative reflexes controlling them, is the presence of cold thermoreceptors involved in nasal patency sensation.

The idea of cold thermoreceptors in the nasal mucosa was proposed several years ago by Eccles [7] who reported that menthol administration, when topically applied, produces the illusion of decongestion and improves nasal airflow without actually altering nasal morphology. Recent studies have shown the presence of TRP (transient receptor potential) M8 channel by immunostaining in human nasal tissue principally in the epithelium, secretory glands, and vessels [8]. The transient receptor potential (TRP) channel superfamily is a nonselective cation channel and can be classified into six subfamilies: melastatin 8 (TRPM8) subfamily is activated by cold temperatures and menthol.

Another recent interesting study has confirmed that air temperature is a contributing factor to the perception of nasal patency, but not the sole factor, as air humidity also contributed significantly [9] suggesting that dynamic mucosal cooling (i.e., heat loss) rather than air temperature alone provides the trigeminal sensation that results in perception of patency. The dynamic cooling, though, is not just a function of the static air temperature or humidity in the environment; it also depends on the interaction between an individual's nasal airway structures (cartilages and mucosa) and the inspired air flow. The quantification of this new parameter "dynamic cooling" may lead to new clinical evaluation tools of nasal patency.

7.2 Nasal Air Flow Test

Traditionally, nasal ventilation is objectively measured by means of active anterior rhinomanometry (AAR) or acoustic rhinometry (AR). Nasal patency can be measured in the actively breathing patient, "the dynamic method," through AAR or passively through AR which uses acoustic reflections from the nasal cavities to study their geometry (minimal cross-sectional areas and nasal volumes) [10]. With AAR, two parameters are recorded: pressure gradient from the nostril to the rhinopharynx and flow. The rhinopharyngeal pressure is measured by sealing of the nostril and measuring pressure through the sealing in the same nasal cavity which, in fact, is not ventilated. Since there is no airflow in the nasal cavity with the sealed nostril, pressure at the nostril is equal to that in the nasopharynx. Since 1984, the permanent Standardization Committee on Rhinomanometry [11] published the following statements to perform rhinomanometry on uniformity: for the pressure gradient measure, the basic method is the adhesive tape technique which gives an airtight seal with a minimal distortion of the nostril and it is easy to perform. The use of a facial mask for the flow is the method of choice: the advantages are minimum to no nasal valve deformation and little chance of leakage at the level of the nostril. However, any kind of mask that does not result in deformation of the nose and does not cause leaks is acceptable. The mask should be transparent so that deformation of the nostril or kinking of the pressure tube can be noted and eliminated. Calibration of equipment is needed, the recording should always be performed during quite breathing, and the patient should be in a sitting position and have a rest and adaptation time to the environment temperature. The $x-y$ recording is considered the best because it shows very well the relationship between pressure gradient and flow. The resistance is preferably expressed at the fixed pressure of 150 Pascal and the flow is expressed in cm^3/s.

However, despite the efforts of the International Standardization Committee, despite the introduction of the computerized analysis of the results and the studies of different authors devoted to solving methodological problems and the realization of technical devices, AAR after more than 35 years since first introduction into clinical practice still represents a topic of discussion to be subjected to a critical review [12].

In fact, for example, the problem of standardization does not end with the reference variables (flow measured in cm^3/s at a fixed pressure of 150 Pa) but includes many aspects that have a decisive influence on the results. Among them, the method

of application of the receptors does not represent a triviality, on the contrary, it constitutes an element of extreme importance for the reliability of the collected data: this delicate phase, key to the entire test, is subjected exclusively to the examiner expertise. Consequently, his/her degree of experience and attention can be variables that can influence the validity of the exam in a positive or negative sense.

The biggest problem, however, is the frequent detection of a discrepancy between the subjective sensation of the degree of nasal obstruction/patency, the objective parameter recorded with rhinomanometry, and the endoscopic picture.

This phenomenon is quite common and, if considered in itself, limits the outcomes of functional surgery: Dinis and Haider [13] reported that patients with significant nasal obstruction have milder degrees of septal deviation, while other patients with severe septal deformities have mild symptoms.

The postoperative improvement in symptoms of nasal obstruction was reported to range between 26 and 94.4% depending on the length of follow-up and the method of assessment of results [14, 15]. Considering subjective instruments of nasal obstruction evaluation (such as the Nasal Obstruction Symptom Evaluation Scale [NOSE]), objective parameters recorded at rhinomanometry or acoustic rhinometry, patient history, and objective examination, it can be generally stated that: when anatomic anomalies on one or both sides are present, the symptom of nasal obstruction is constant, and the inspection determines the kind and location of the stenosis; nasal allergy or vasomotor rhinitis are mostly characterized by alternating nasal obstruction, at history and inspection non purulent secretion and irritation can be recorded whereas rhinomanometry with nasal decongestion test determines the degree of the mucosa swelling of turbinates.

Atrophic rhinitis is defined as "a chronic debilitating disease of the nasal passages that is characterized by progressive nasal mucosa atrophy, nasal crusting, fetor, and enlargement of the nasal space with paradoxical nasal congestion" [16]. In this case, the discrepancy between the subjective sensation, the objective parameters, and the endoscopic picture is so evident (Fig. 7.3) that the symptom is defined

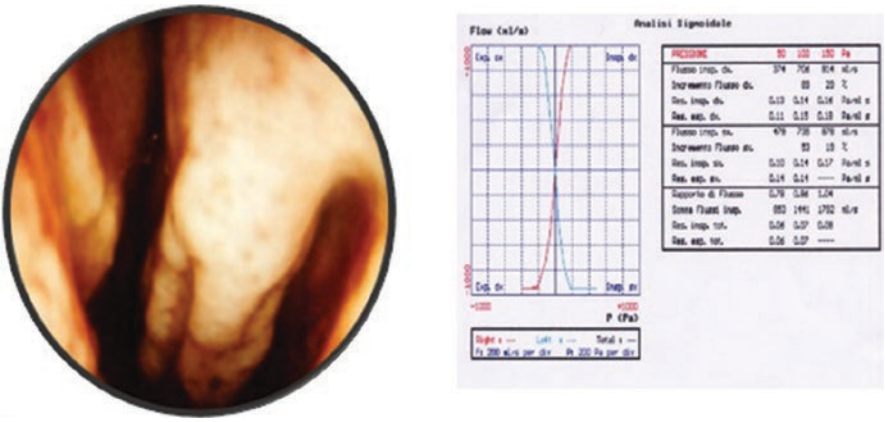

Fig. 7.3 Endoscopic view of inferior turbinate atrophy and the corresponding rhinomanometric picture

as "paradoxical congestion." However, the fact that the patient's subjective complaints of nasal obstruction or shortness of breath cannot be verified objectively does not mean they are not real and valid symptoms originating from a physical abnormality. In fact, reconsidering the principles of nasal physiology and the physical laws outlined so far, it is equally evident that the atrophy of the nasal mucosa, altering the structures and dynamics involved in the nasal valve area, does not allow it to convey the inspired air according to laminar flows. The turbulent flows that pass through too wide nasal fossae, give rise to the sensation of obstruction worsened by the loss of the trigeminal thermoreceptors essential for the normal sensation of airflow. Thus, the complaint of nasal obstruction in patients suffering from atrophic rhinitis is real and is due to actual loss of sensory nerves associated to the atrophy of nasal turbinates: in this case, the determination of the mucociliary transport time or the newly suggested parameter of dynamic cooling may represent other clinical evaluation tools of the atrophic mucosa and the feeling of nasal obstruction.

Recently, the use of four-phase rhinomanometry (4PR) has been recommended for the assessment of nasal obstruction. In this method, the nasal airway resistance is calculated using hundreds of resistances continuously recorded during the whole breathing cycle [12]. In 4PR, one of the most important parameters to be considered is the effective resistance of the entire breath (Reff) and its logarithmic value (logReff). An advantage of 4PR is that a result can be obtained for all patients, as it is not necessary to reach a designated pressure on the pressure–flow curve [17]. Two different studies compared 4PR and PNIF in the study of rhinological patients finding the two instruments to be comparable in results, with PNIF correlating better than 4PR with the nasal symptoms. Both studies concluded that PNIF, being inexpensive, fast, portable, simple, and reliable, has practical advantages over 4PR and should be available in daily practice for the assessment of nasal obstruction [18, 19].

Although recently it has been proposed that the sensation of nasal obstruction reported by patients with empty nose syndrome may be more related to an impaired trigeminal function rather than to a mere nasal airflow obstruction, yet the measurement of nasal resistances/flows can still be important in these patients to demonstrate the absence of obstruction [20, 21].

To the best of our knowledge, no studies have been performed using either PNIF or 4PR in patients affected by atrophic rhinitis, instead there are studies conducted in patients with atrophic rhinitis/empty nose syndrome using classic RM.

RM has been used to study the effects of partial middle turbinate resection on nasal resistance measured by means of AAR. Cook and coworkers observed significant reduction of nasal resistances together with a significant increase of nasal airflow in these patients. Anyway, no evaluation of subjective symptoms was considered [22]. Considering the consequence of turbinate surgery, anyway, atrophic rhinitis should be more expected in the cases of inferior turbinectomy [23]. On this regard, Passali and coworkers, evaluating the effects of different treatments of the inferior turbinate hypertrophy, observed that inferior turbinectomy was associated with the development of atrophic rhinitis in 22% of the 45 patients treated with this surgical technique who showed a disruption of mucociliary clearance, lower IgA secretion rates, and curtailment of general heating and humidification capacities, although

AAR results showed a great effect on nasal obstruction. The authors concluded that possibly the increased nasal airflow obtained by inferior turbinectomy could produce excessive drying of the nasal secretions and crusting [24].

RM has been used also to evaluate the effects of nasal treatments in patients with atrophic rhinitis. Very recently, Testa and coworkers, evaluating the effects of α-tocopherol acetate in patients with atrophic rhinitis also by means of AAR, observed a significant increase of nasal airflows demonstrating the utility of AAR in the study of these patients [25]. In a comprehensive review on the surgical procedures used for the empty nose treatment, Leong concluded that given the complexity of the condition and the high degree of failure (up to 21% of patients may report only marginal improvement), before undertaking any surgical procedure in these patients, along with the subjective evaluation also an objective measurement of nasal resistances should also be performed in order to demonstrate the effects of the surgery [26].

7.3 Olfactometric Techniques in Atrophic Rhinitis

The term dysosmia indicates the alteration of smell due to diseases of the peripheral or central structures. We have two different kinds of damage, one based on quality and one based on quantity, so we have two different types of dysosmia too. The quantity dysosmias are divided into: *hyposmia, anosmia*, and h*yperosmia*. The quality dysosmias are divided into: *parosmia*, *cacosmia*, *phantosmia*, and *presbyosmia*. The quantity dysosmias (in particular hypo-anosmias) are the largest part of dysosmias. The hypo-anosmias are classified into central and peripheral, and anosmias in particular are also divided into mechanical and perceptive anosmias. *Mechanical anosmias* are those that, despite the integrity of the neuroepithelium, respiratory, and olfactory centers, can be determined by inflammation of the nasal mucosa or defective ventilation, or any pathological process that can hinder the arrival of the gas molecule carrier to the peripheral receptor. The *perceptive anosmias* are secondary to alterations of neuroepithelium, olfactory tract, and olfactory centers, and they can be pure forms, which become mixed when they coexist with obstructive mechanical forms. We support the hypothesis that olfactory alterations due to atrophic rhinitis have to be classified as mixed forms. Dysosmias may also occur in patients who are affected by psychic alterations, or chronically exposed to chemical substances that may cause mucosal or nervous lesions (professional dysosmias). There are also several syndromes and diseases that may be related to an important loss of smell, such as congenital agenesis of the olfactory nerve (which can often be associated with the agenesis of the trigeminal nerve), Klinefelter syndrome, Turner syndrome, von Willebrand syndrome, and Kallmann syndrome. Dysosmia can also occur because of careless medical and surgical maneuvers that can cause ethmoidal fractures, deviations of the nasal septum, post-traumatic atrophic rhinitis, cicatricial stenosis and bridles, and alterations of the olfactory mucosa in general [27, 28]. Many medicaments can provoke dysosmia, such as nasal sprays containing tyrothricin, neomycin, or chemicals like acetylcholine and vasoconstrictors as well as antihistaminic, morphine, streptomycin.

A systematic revision of olfactometric techniques (studied for more than 40 years) is far to be definitive while objective olfactometry remains a distant goal [29].

From the point of view of our group's personal experience, we would like to underline how it is fundamental to perform subjective olfactometric tests together with the study of radiological images, rhinofibroscopy, and nasal function tests with the nasal decongestion test that allows to differentiate the transmission and/or mixed alterations from sensorineural forms.

We use the Sniffin' Sticks® olfactory test (Burghart instruments, Wedel, Germany) for performing the threshold, detection, and identification test. All these tests were preceded by a complete nasal functionality testing, and in particular we never forgot to perform rhinomanometry to measure the airflow and resistance of nasal cavities and sensitized with nasal decongestion (realized by spraying two puffs per nostril of a nasal decongestant with short latency of action, naphazoline), in order to allow a correct odorants' diffusion to olfactory epithelium. Odorants were presented in felt tip pens. The pens have a length of approximately 14 cm and an inner diameter of 1.3 cm. Pen's tip is filled with 4 mL of liquid odorant, or odorants dissolved in propylene glycol. For odor presentation, the cap was removed for 3 s and the pen's tip was placed at a distance of approximately 2 cm from both nostrils. Odor thresholds for n-butanol were assessed using a single staircase, three-alternative forced choice (3-AFC) procedure. Sixteen dilutions were prepared in series starting from a 4% n-butanol solution (dilution ratio 1:2 in deionized water as solvent). Three pens were presented in randomized order, two containing the solvent and the third containing the odorant. Patients had to identify the odor containing pen. Triplets were presented at intervals of approximately 20 s. Reversal of the staircase was triggered when the odor was correctly identified in two successive trials. Threshold was defined as the mean of the last four of eight staircase reversals. The subjects' scores ranged between 0 and 16. In the odor discrimination task, again using a 3-AFC, triplets of pens were presented in randomized order, with two containing the same and one a different odorant. Subjects had to determine which of the three pens smelled different. Triplets were subsequently presented with a 20–30 s interval between them; the interval between the presentation of individual pens was approximately 3 s. Because 16 triplets were tested, the subjects' scores ranged from 0 to 16. When measuring odor thresholds and odor discrimination, subjects were blindfolded to prevent visual identification. Odor identification was assessed for 16 common odors. Using a multiple-choice task, identification of individual odors was performed through lists of four descriptors each. The interval between odor presentations was 20/30 s. Again, the subjects' scores ranged from 0 to 16. Finally, we calculated the TDI score (threshold discrimination identification) with a range from 0 to 48. TDI values <15 identify an anosmic subject while values <5 must not be considered as reliable [30].

Regarding olfactive impairment in atrophic rhinitis, even if it is often described, very few studies were conducted and fewer again have a well-designed protocol. In particular, Huart in 2012 [31] tested nine patients: psychophysical testing (both

orthonasal and retronasal) of the olfactory function was performed with the Sniffin' Sticks tests, and chemosensory function was also assessed (both orthonasal and retronasal) with chemosensory, late near-field ERP elicited with relatively specific olfactory (2-Phenyl ethyl alcohol) and trigeminal stimuli (CO_2). They conclude that the loss of olfactory function may result from a multiplicity of reasons, in particular the absence of trigeminal ERP responses might be explained by the resection of the inferior and/or middle turbinate; moreover, objective impairment of the sense of smell in patients suffering from AR using chemosensory testing and ERP was well demonstrated and the authors stated that this is an additional argument to state that radical surgery and particularly turbinectomies should not be performed to treat nasal obstruction.

In our experience, olfactory impairment is always reported by patients suffering from AR as the paradoxical nasal obstruction, the changing in nasal airflow, the nasal mucous dehydration, and the consequent epithelial metaplasia are the pathogenic roots of this common symptom. The showed alteration of the retronasal olfaction is the reason why the dysgeusia is also present.

From a medico-legal point of view, we recommend to perform subjective olfactory testing after mucociliary transportation time elevation and after anterior active rhinomanometry in order to have a more objective diagnosis [32, 33].

7.4 Conclusions

Empty nose syndrome (ENS) is a disorder with a potential paradoxical obstruction phenomenon. However, the degree of clinical correlation is unclear, since only a very small subset of patients that undergo radical resection develop long-term complications, suggesting that there are additional genetic and environmental factors at play. The etiology of ENS remains undefined and the inability to diagnose it objectively has fueled further speculation that it could be linked to nasal neuropathy or psychosocial factors. ENS remains a controversial topic that deserves further scrutiny with prospective studies that include long-term observations.

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Computational Fluid Dynamics: Is It Possible to Produce a Real Model of the Nasal Flux?

8

Barbara Flora, Paolo Di Nardo, Francesco Maria Passali, Mariapia Guerrieri, and Stefano Di Girolamo

Abbreviations

CFD	Computational fluid dynamics
ENSQ6	Empty nose syndrome 6-item questionnaire
NO	Nasal obstruction
PNIF	Peak nasal inspiratory flow
SNOT	Sinonasal obstruction test
VAS	Visual analogue scale

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8.1 Introduction

Chronic nasal obstruction is a very common symptom that affects nearly 10–20% of patients worldwide [1]. The cause of nasal obstruction is numerous: septal deviation, turbinate hypertrophy, allergic rhinitis, or empty nose syndrome. Nowadays there are no objective standardized methods to demonstrate the site and grade of obstruction.

Imaging from CT scan or MRI shows the nature of nasal obstruction but does not consent to quantify it in terms of air flux.

NO may be evaluated using subjective assessment tools (visual analogue scale, symptom score, standardized questionnaires) or by objective estimation (active anterior rhinomanometry, acoustic rhinometry, peak nasal inspiratory flow).

In daily practice, the most common method to define nasal obstruction is the subjective evaluation through questionnaires regarding nasal symptoms or quality of life (SNOT, ENSQ6, VAS) [2].

Objective measurements like anterior rhinomanometry, acoustic rhinometry, and peak nasal inspiratory flow (PNIF) are the most diffused tools [3].

8.2 Current Methodology to Evaluate Nasal Resistance and Patency

These tools can estimate the grade of obstruction but they have several contestable points. If we analyze each method, we can notice that there are missing points:

8.2.1 Rhinomanometry

Rhinomanometry is used to measure nasal pressure and airflow during breathing. It is accepted as the standard technique to measure nasal airway resistance and to assess the patency of the nose. It gives information about total nasal resistance, but it provides no information about the singular nasal fossa. It is not possible to evaluate the valvular collapse. The measuring process requires some practice and its results are performer-dependent, which means they are not standardized or comparable [4].

One of the most critical issues is the lack of correlation between patients' symptoms and objective measurements. This is particularly important in the case of patients suffering from empty nose, where the nasal resistances are low but the main complaint is about what is called paradoxical nasal obstruction [5].

Probably the "paradoxical obstruction" in patients who suffer from ENS is caused by the flux alteration secondary to medial or lateral nasal wall demolition. The anatomic changes in nasal mucosa lead to turbulent fluid dynamics patterns that determine an alteration in nasal mucosal receptor stimulation. This particular condition can be evaluated in a precise way using CFD (Fig. 8.1).

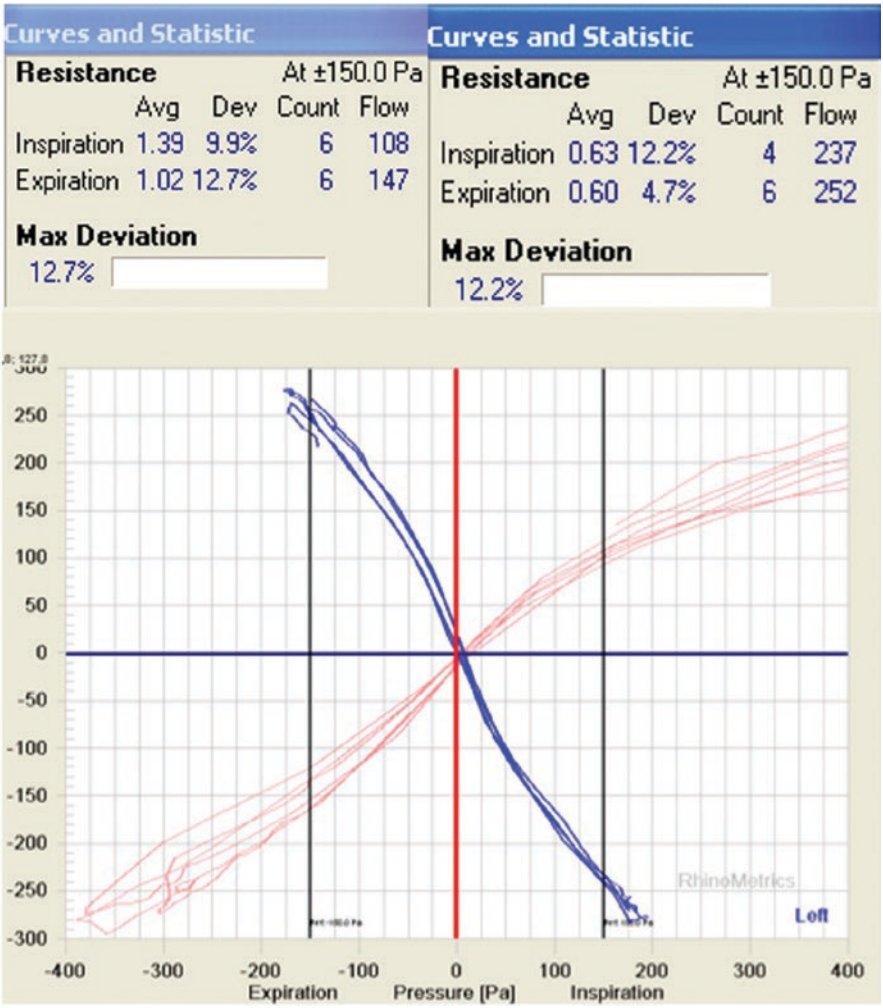

Fig. 8.1 Example of anterior rhinomanometry

8.2.2 Acoustic Rhinometry

Augé et al. stated, "Acoustic rhinometry is quick and easy to perform, without the need of patient collaboration. It was standardized in 2005 by the Standardization Committee on objective assessment of the nasal airway of the European Rhinology Society" [6].

Acoustic rhinometry is an easy, noninvasive, and non-painful procedure to perform that uses the reflection of sound signal to measure cross-sectional area and volume of the nasal fossae. Acoustic rhinometry provides an anatomic description of the nasal passage, whereas rhinomanometry offers a functional measure of the

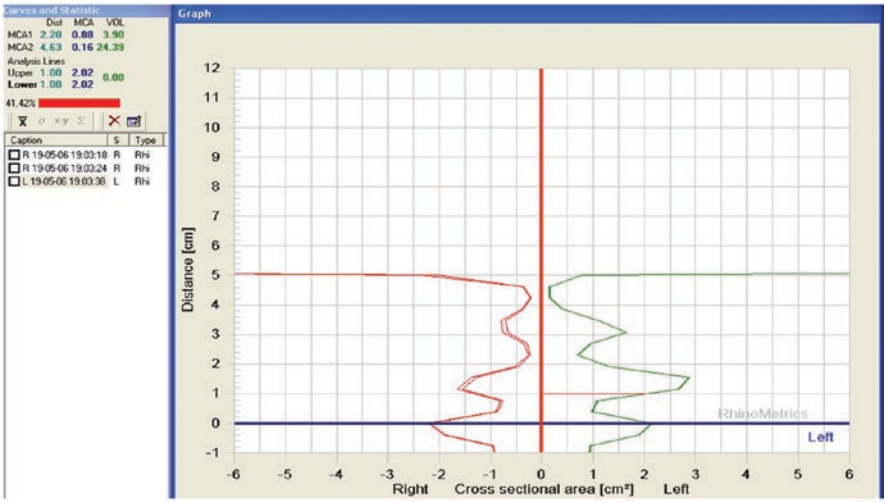

Fig. 8.2 Example of acoustic rhinometry

pressure–flow relationships during the respiratory cycle. It is useful to study anatomical landmarks or to verify the airway changes in response to drug administration. The principle used in this test is the reflection of acoustic waves generated from a speaker and conducted to nasal fossa along a tube. The sound pulse is reflected back to a microphone and the delay time of reflection is registered by a PC that processes it in a graph.

This measurement correlates well with the data from CT scan and the airway resistance measured by rhinomanometry, but when the mucosa is congested or there are nasal polyps sometimes the measurements are not reliable.

The graphic analyzes the entire airway demonstrates the location and severity of the obstruction and evaluates the success of treatment and outcomes [7].

Main advantage of this procedure is that it is noninvasive and it provides a measure of nasal cross-sectional area with the length of the nasal passage in real-time data. This can be done in the office, or in hospital. This cross-sectional area can also be expressed as nasal volume along the nasal passage from the inferior turbinate to the 7 cm area of the nose before the merging of the two nasal passages into one (Fig. 8.2).

8.2.3 Peak Nasal Inspiratory Flow

PNIF has been presented since the introduction of measurement of mouth peak expiratory flow (PEF), a useful tool to monitor airway narrowing in asthma, with the purpose to assess nasal patency. Peak nasal flow can be measured during inspiration (PNIF), by means of a portable flow meter such as the Youlten peak flow meter (Clement Clarke International), and/or expiration (PNEF), by means of a mini Wright peak-flow meter.

The measurement consists of a face mask which the patient applies over the nose (without touching it) with the mouth closed. The patient must be encouraged to inhale as hard and as fast as he can through the mask, keeping the mouth closed starting from the end of a full expiration (residual volume method). Three satisfactory maximal inspirations are usually obtained and the highest of these results is taken as the PNIF. PNIF should be measured in the standing position because PNIF measures, as PEF measurements, are higher when standing than sitting PNIF especially in females. PNIF increases with practice, particularly after the first attempt, so it is important to allow the patient a few tries before taking the three measurements. It is an inexpensive, fast, portable, and simple technique, which does not depend on computers to analyze the data. It has a good reproducibility with a correlation coefficient up to 92% and it consents to measure nasal flow with a direct correlation of nasal obstruction [8] (Figs. 8.3 and 8.4).

Fig. 8.3 Mini Wright PNIF meter

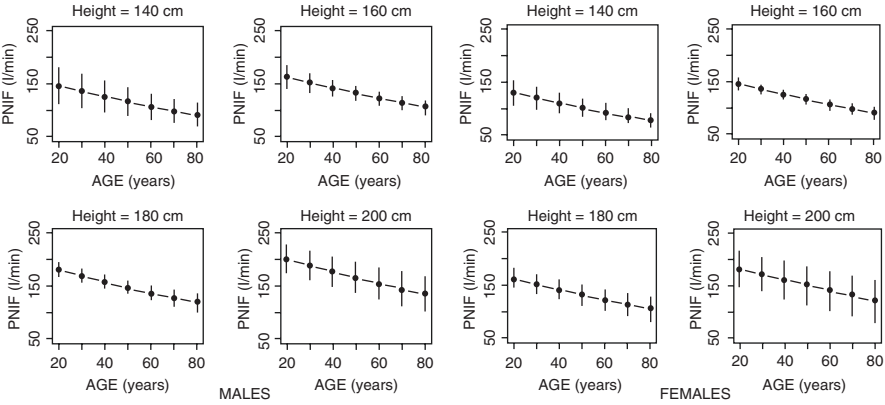

Fig. 8.4 Mean estimates of PNIF of North European Caucasian males and females with specified age (years) and height (cm)

8.3 CFD: Computational Fluid Dynamics

Considering these analyses, it is easy to understand that there is a lack of standardization of objective measurement of nasal patency and obstruction.

In this context, the computational fluid dynamics science has been emerging in the last 25 years, when the first paper was published.

This technology is based on the use of engineering science applied to nasal fluid dynamics, and it allows to create a numerical simulation of nasal flow obtained by data analysis, based on patient CT scan.

The application of CFD is already diffused in other medical fields, for example, in cardiology and even to plan surgical simulation (virtual surgery), especially in maxillofacial surgery [9].

This methodology, using specific software (Mimics; GAMBIT; ITK-SNAP, etc.) [10, 11], consents to obtain a valuable 3D reconstruction of the nasal cavities, then the use of fluid analysis software consents to simulate the nasal flow. Moreover, using mathematical models (Navier–Stokes equation), it is possible to reproduce with good capability the nasal flux in a steady state [12].

We can evaluate different variables that were not considered before like the wall shear stress (WSS)—the friction caused by the air flux on nasal mucosa—; the velocity of flux; and temperature and humidity of the nasal mucosa and air pressure. Different studies demonstrate the comparability of results obtained with CFD simulation and with rhinomanometric data in terms of nasal resistance [13]. These parameters represent new variables that enlarge our knowledge on nasal behavior, enriching our understanding of the mucosal reaction to drugs or consenting us to simulate and predict surgical outcomes.

Although this is an uncontestable point, the CFD still struggles to become a regular clinical tool, in fact a European position paper does not yet consider it a valuable

and comparable method. CFD requires a complex and time-consuming process to obtain results and to plan a simulation.

The methodology requires an advanced engineering software: the most used one is FLUENT by Ansys 19.1; a newer one is Diana [14].

Given the increasing popularity of the CFD in the latest years, medical doctors and engineers are cooperating to develop a software that is easier to use.

8.3.1 Our Review About the Use of CFD in Assessing Nasal Surgery and Future Perspectives

To better understand the state of art of CFD in nasal field, we conducted a review of the literature.

The objective was to understand how the use of CFD in nasal measurement can help otolaryngologists during the preoperative planning and to predict postoperative results.

From November 2019 to March 2020, three different people searched PubMed using as keywords: CFD, computational fluid dynamics, and empty nose syndrome. The search was focused on those articles which collected data of patients who underwent nasal surgery (septoplasty or turbinoplasty) because of nasal obstruction. The main exclusion criterion was the year of publication: articles published before 2005 were not included. 357 articles were selected and published from 2008 to 2020, and 50 of them deserved our attention. Analyzing the articles selected, focused on the latest CFD techniques, we gave particular attention on the possibility of surgery simulation. The newest CFD software, in fact, consent to build from CT scans a three-dimensional view of patients' nasal fossae. Hence it is possible to virtually perform and compare different kind of operations, in order to predict the most effective outcome in terms of nasal airflow [15].

This procedure is still complicated, yet challenging, and the results are encouraging. The first article about this kind of nasal virtual surgery in healthy subjects was published by Zhao and Jiang in 2014 [16] (Fig. 8.5).

The use of CFD for virtual surgery, in the future, would allow surgeons to perform a real patient-designed nasal surgery [17]. At this regard, Burgos et al. in 2018

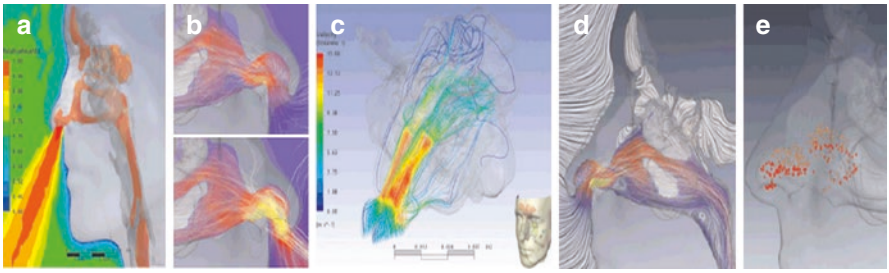

Fig. 8.5 Example of nasal flux evaluation with computational fluid dynamics. (**a**) Temperature; (**b**) velocity; (**c**) flow distribution in the nose and paranasal sinuses; (**d**) flux direction; (**e**) pressure

have already developed an integrated computational platform to perform surgery simulation to obtain the best results [18, 19]. Moreover, virtual surgery would not only be crucial in the preoperative counseling and planning but would also be used as a brand-new tool for teaching models. It must also be taken into account the possibility to use the 3D model of the nasal fossae to correlate symptoms with the anatomy of the selected patient, in order to discriminate organic pathologies from functional ones or even from psychological disorders [20].

The modern research goal is to obtain, through CFD-based 3D model of the nasal cavities, the possibility to create a dynamic mash motion, based on the evaluation of different variables, which could reproduce the physiological variation of fluids during the respiratory dynamics. That is a big challenge but it is fundamental to better understand nasal respiratory cycle and the influence of the nasal valve collapse and the alae nasi collapse on it. This information would improve the analysis of drug delivery and deposition rate and mucous dissolution, giving more information on the mechanic of mucociliary clearance [21].

In the next future, it is desirable to create a big-data computational storage through which it would be possible to realize an artificial neural networking, in order to provide rapid and alternative CFD solution that would eventually simplify the decision-making process.

Connecting this network to a machine learning surgical robot could also lead, through the use of digital twin technology, to a new era of personalized medicine, with better standardized surgical procedures and predictable results [22].

8.3.2 Limitation

Firstly, because of radiation, not every patient suffering from nasal obstruction undergoes CT scan. Secondly, CFD measurements still require a considerable amount of time, in the presence of an IT specialist, able to use software which are still far from being doctor-friendly.

It must also be noted that mathematical formulas and computer analysis cannot yet predict variables like: the capability of surgeon, the mucosal healing process, and the subjective perception of nasal obstruction. These factors are different for each case and they constitute, this far, unpredictable, yet crucial variables that lead to the final outcome.

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9 Imaging: The Role of CT Scan, Cone-Beam and MRI in the Diagnosis of Atrophic Rhinitis

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9.1 Introduction to Diagnostic Imaging Examination in Atrophic Rhinitis

Atrophic rhinitis (AR) is a condition characterized by extensive atrophy of nasal mucosa associated with bone erosion and consequent cavity enlargement [1].

Concerning the etiology, AR can be a primitive (PAR), also called Ozaena, or secondary (SAR) due to various predisposing conditions (nasal surgery, head radiant therapy, traumas, infective, granulomatous, or other systemic diseases) [2]. Clinical presentation includes nasal obstruction, impaired obstruction, crusting, and epistaxis. The diagnostic assessment involves a deep and precise objective and endoscopic examination and eventual diagnostic imaging to confirm the clinical suspect [3–5].

In the study of the nasal cavities, diagnostic imaging assists the ENT specialist, allowing him to obtain additional information supporting clinical evaluation. For this reason, it is mandatory to first perform the clinical and rhinoscopic exam and then, based on the obtained findings and suspected pathology, to choose the most appropriate imaging technique [5].

Radiological examinations not only add key diagnostic data but also help ENT specialists planning of both clinical and surgical treatment, providing a complete visualization of regional bone anatomy, of mucous membranes and soft tissues and therefore a clear determination of the exact extent of disease and the possible involvement of adjacent structures, not always clinically evaluable. Moreover, imaging serves as a real-time guide during surgical treatments. In specific conditions, during endoscopic surgery, it is possible to adopt a synchronized imaging-guided system that provides a real-time anatomical navigation with a complete

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and panoramic view of the cavities, which is particularly useful when anatomy is subverted due to previous surgery, accidental trauma, or developmental abnormalities [6].

Imaging is also essential to define the precise extension of pathological alterations and allows to evaluate the effectiveness of surgical and/or medical treatments, as well as to provide a follow-up with clear determination of possible disease progression [7].

9.2 Diagnostic Imaging in Atrophic Rhinitis

Currently, the diagnostic imaging techniques available for the study of the nasal cavities include plain radiology, multi-slice CT (MSCT) and cone-beam CT (CBCT), which are the true diagnostic gold standards, and magnetic resonance imaging (MRI).

Traditional X-rays of the nasal cavities represent a first-level study, widely diffused and accessible. It is a suboptimal imaging tool for the diagnostic process and follow-up of atrophic rhinitis due to the low anatomical resolution of such complex, bone-dense areas as the nasal cavities [8].

9.2.1 Computed Tomography in Atrophic Rhinitis

The improvement of performance and development of more efficient machines for computed tomography seen in the last years, led to the achievement of high-quality three-dimensional images in very short time.

MSCT scan offers valid spatial and morphological differentiation of structures and tissues and has high accuracy, sensitivity, and specificity in characterizing paraphysiological and pathological anatomical variation. It allows the inclusion in studies of large body volumes, with a spatial resolution smaller than 1 mm. For the study of the nasal cavities, the patient must be placed on the gantry table in prone position with the head entering the gantry first. The area of scan should be settled based on the projection of the head in order to include the roof of frontal sinus and the whole hard palate. Axial and coronal sections with 3 mm thick slices should be performed obtaining high-quality 2D images (Fig. 9.1). Axial sections should be parallel to the hard palate. The study should be completed with sagittal reconstructions [9] and with the elaboration of 3D images based on the 2D acquisition (Fig. 9.2).

MSCT scan remains a rapid and accessible technique, being well tolerated by patients of a wide range of age, and even in critical clinical conditions [8].

However, the radiation dose (even if quite limited with the most recent machines, accounting to 990–1160 μSv) and the costs associated with CT scans make the use of this examination inappropriate as a first-line diagnostic tool [10]. The necessary course implies a preliminary diagnosis based on the anamnestic record, clinical symptoms, and endoscopic evaluation, which, if suggestive enough, can provide indication to a confirmatory CT scan. In fact, it allows a fine visualization of

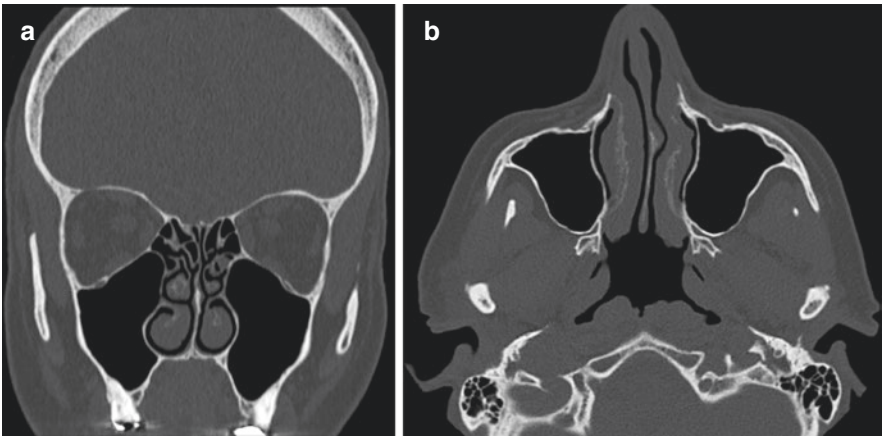

Fig. 9.1 Coronal (**a**) and axial (**b**) CT images of normal nasal cavity

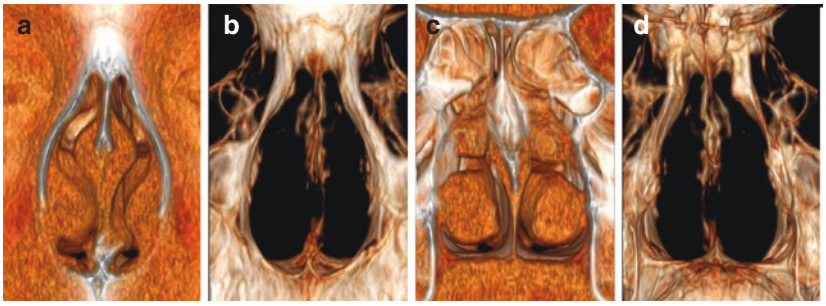

Fig. 9.2 3D reconstruction of a normal nasal cavity showing anteroposterior view (**a** and **b**) and posteroanterior view (**b** and **c**), with different thresholds to allow evaluation of soft tissue (**a** and **c**) and bone structures (**b** and **d**)

intranasal osteochondral and mucosal structures such as the sinonasal walls and turbinates, and it can both confirm endoscopic findings and give information for the etiological differentiation of different conditions [10].

Cone-beam is a CT scanning technique consisting in a rotating gantry and 2D-detector producing one volumetric scan of the target. Differently than traditional CT acquisition, where final multiplanar views are reconstructed combining the single slices, CBCT allows a direct 3D imaging [11]. The technique allows for the use of smaller and less-expensive machine components (no patient movement required during acquisition), more efficient X-ray utilization as well as a lower dose administration (68–368 μSv instead of 990–1160 μSv), and energetic consumption, consistently reducing costs [12, 13]. However, scanning time is not so short, and the acquisition quality is influenced by even the tiniest movement; this makes this technique especially appropriate for the study of head structures, which are sufficiently immobile but may be unsuitable for uncompliant patients, such as

children or those affected by cognitive impairment or movement disorders [14]. Moreover, the scanning is influenced by metal-related artifacts, with a consistent loss of anatomical resolution of the tissues adjacent to the metallic body. This is particularly crucial in determining the diagnostic power of this technique for oral and nasal cavity pathology, being these regions composed by small, closely connected structures [15].

9.2.1.1 Indications to Computed Tomography in Atrophic Rhinitis

In suspected AR, a CT scan (either MSCT or CBCT) of nasal cavities should be performed based on strong clinical suspicions such as [3–5]:

- Signs of chronic rhinosinusitis, *dry nose* syndrome:
  - Nasal obstruction
  - Dry mucosa
  - Nasal crusting
  - Epistaxis
  - Impaired olfaction including cacosmia
  - Itching or burning sensation, nasal pain
  - Sensation of midface fullness
- History and SAR associated diseases and conditions:
  - Nasal surgery
  - Head radiotherapy
  - Cocaine addiction
  - Exposure to caustics
  - Sarcoidosis
  - Wegener's granulomatosis
  - Tuberculosis
  - Cryoglobulinemia
  - Cicatricial pemphigoid
  - Behcet's disease
  - Relapsing polychondritis
  - Sjögren's syndrome
  - Crohn's disease (extraintestinal form)
  - Cystic fibrosis
  - Stewart's granuloma
  - Syphilis
  - Leprosy
  - Leishmaniasis
  - Rhinoscleroma
  - Ectodermal dysplasia
- Endoscopic suggestive findings:
  - Nasal cavities enlargement up to the choanae
  - Mucosal alteration (dryness, atrophy, dystrophy, ulceration, crusting)
  - Turbinate and nasal wall destruction or hypoplasia
  - Post-surgical structural alterations

- Septal discontinuity
- Erosions involving mucosal and osteochondral structures
- Synechiae
- Nodular alterations

9.2.1.2 Computed Tomography and Cone-Beam Computed Tomography Findings in Atrophic Rhinitis

- Radiological findings of AR (Fig. 9.3) [4, 5, 16–18]:
  - Thickening of the mucoperiosteal structures inside the paranasal sinuses (stars in Fig. 9.3b)
  - Destruction of osteomeatal complex, which is no longer definable secondary to reabsorption phenomena
  - Maxillary sinus hypoplasia
  - Nasal cavity enlargement with erosion of lateral nasal wall (arrow in Fig. 9.3a)
  - Bone destruction and mucosal atrophy in the inferior and middle turbinates (arrowhead in Fig. 9.3a)
- Even if less common, the following findings might be seen in case of SAR [3]:
  - Inferior turbinectomy nasalization: post-surgical patients
  - Osteochondral and mucosal atrophy and synechiae: sarcoidosis
  - Bony and cartilaginous erosion osteosclerosis: Wegener's granulomatosis
  - Extensive mucosal and bone destruction, granulomas: Sinonasal tuberculosis
  - Destruction of cartilaginous structures: Relapsing polychondritis

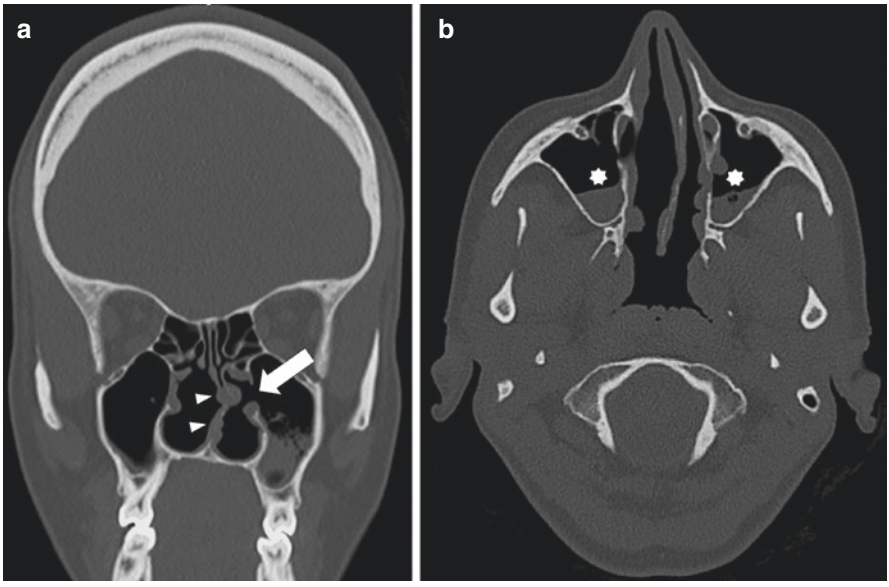

Fig. 9.3 Coronal (**a**) and axial (**b**) CT images of a patient with atrophic rhinitis showing the absence of inferior and middle turbinates (arrowhead) with voluminous nasal cavities, mucosal thickening of the paranasal sinuses (stars) with erosion of lateral nasal wall (arrow)

- Extensive destructive lesions of turbinates, sinonasal walls, septum, and nasal pyramids: Chron's disease
- Mucosal hyperplasia/nasal polyposis: Cystic fibrosis
- Extensive destruction of adjacent structures such as the orbits: Stewart's granuloma
- Bony remodeling extended to skull base: postradiation therapy
- Synechiae of the nose and nasopharynx: caustic

9.2.2 Magnetic Resonance Imaging in Atrophic Rhinitis

Magnetic resonance imaging, both with and without intravenous administration of gadolinium DTPA (GD), has allowed acquisition of detailed images of the paranasal sinuses, providing additional information on the soft tissues contained in them and possible involvement of local structures which cannot be evaluated clinically, by pathological processes. Bone structures are thus more adequately studied with CT scan [19].

The static magnetic field (CMS) and radio-frequency pulses of MRI induce movements of protons inside the molecules. These perturbations and oscillations occur in different times and ways based on the structure of the investigated tissues and provide data necessary for the production of images on multiple planes of the space and with different signal characteristics as a function of the radio-frequency pulse sent. The nasal mucosa, being highly vascularized, has signal characteristics similar to an edematous epithelium (hyperintensity of the signal in T2 SE-weighted images), a characteristic that allows to clearly differentiate it from pathological alterations [20].

Acquisition protocols include T1- and T2- weighted images, with adipose tissue signal suppression which also increases the contrast resolution of the images obtained. The study should be performed in the three planes, with an average thickness of 3 mm [21] (Fig. 9.4).

In the case of AR, the MR examination confirms the atrophy of the nasal turbinates and highlights the widening of the nasal cavities associated with bone erosion and convexity of nasal lateral walls. The mucosal layer is clearly visible and tends to be reduced in this condition; also, the presence of blood deposits can be highlighted [22] (Fig. 9.5).

However, not all patients are eligible for this study: MRI-incompatible metal devices or severe claustrophobic disorders may contraindicate it. Another limitation, especially in the study of the nasal cavity, is the presence of metal dental implants, which determine severe artifacts especially when high magnetic fields (1.5–3 T) are used. Moreover, the quality of images obtained is strongly influenced by movement, being easily invalidated if the patient cannot maintain adequate stillness during the acquisition time which lasts for about 30 min.

Although MRI may represent an alternative to the CT examination in same occasions, particularly in young subjects in order to avoid exposure to radiation, the long acquisition times and costs of the examination, higher than those of the CT exam, make it a second-level exam in the diagnostic process of AR.

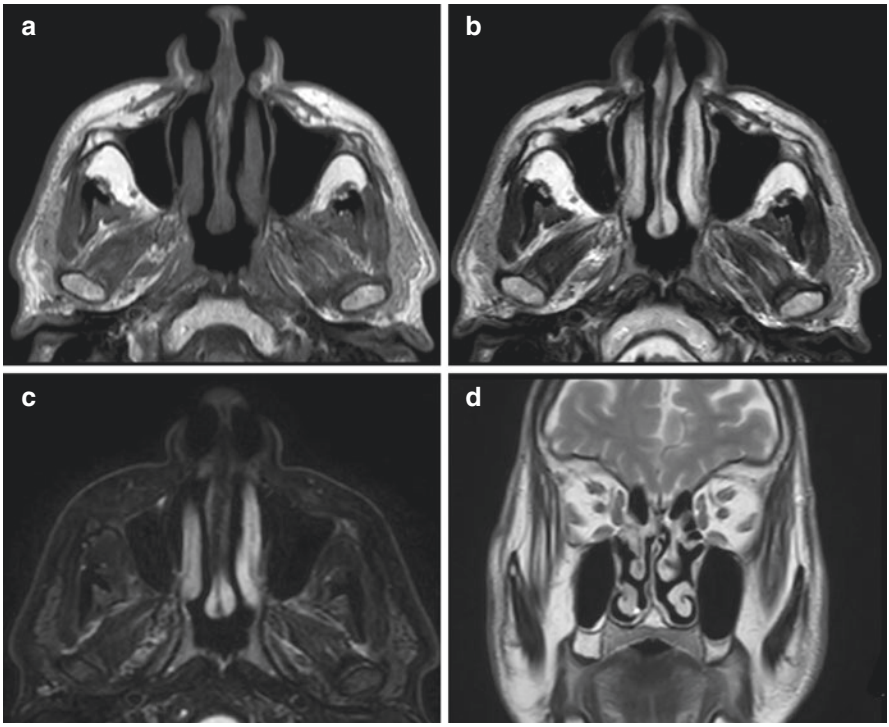

Fig. 9.4 Standard MRI images of a normal nasal cavity showing axial T1-weighted (**a**), axial T2-weighted (**b**), axial T2-fat-sat (**c**), and coronal T2 weighted (**d**) images. These sequences allow evaluation of the normal mucosal thickness and signal intensity (high T2w signal) and detailed anatomy of turbinates

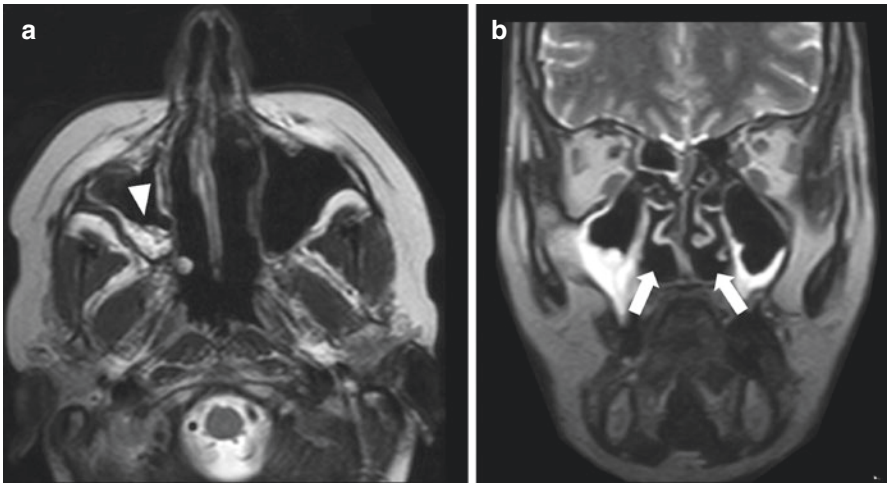

Fig. 9.5 Axial (**a**) and coronal (**b**) T2-weighted images of a patient affected by atrophic rhinitis showing absence of inferior turbinates (arrows), a nasal cavity enlargement and thickening of paranasal sinuses mucosae

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Part IV

Treatment of Atrophic Rhinitis

Atrophic Rhinitis: Medical Treatment

10

Codrut Sarafoleanu and Elena Patrascu

10.1 Definition

Atrophic rhinitis (AR) represents a chronic disease, of unknown etiology, with a progressive atrophy of the nasal mucosa and the turbinate bone. Consequently, fetid secretions can appear in the nose, with a specific foul smell (ozena), nasal obstruction or nasal crusting, epistaxis, smell loss, and halitosis. If the disease progresses chronic pharyngitis, otitis media with effusion or nasal deformity can also occur [1]. The incidence in general population is between 0.3 and 7.8%, depending on the country, with higher incidence in Asian territories [2, 3]. It was Fraenkel who, in 1876, first described the entity called atrophic rhinitis, defined by nasal crusts and atrophy of the nasal mucosa, along with a specific smell triad [4, 5].

10.2 Etiology

Nowadays, in most cases of atrophic rhinitis, the diagnosis is an exclusion one. Theoretically, the authors divide the etiology of the disease in two categories: primary, in which the disease appears de novo, and secondary atrophic rhinitis, where the affection develops as a consequence of other primary diseases [6].

The etiologic agent in most cases of primary atrophic rhinitis is thought to be the infection with *Klebsiella ozaena* [6]. There are other factors, such as hereditary diseases, chronic rhinitis or rhinosinusitis, nutritional loss, and autoimmune diseases. Other bacterial agents involved in the etiopathogenesis of atrophic rhinitis are *Pseudomonas aeruginosa*, *Coccobacillus foetidus-ozaenae*, *Diphtheroids bacillus*,

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Haemophilus influenzae, *Bacillus mucosus* or *pertussis*, and *Proteus* species [4, 7–10].

Secondary atrophic rhinitis is determined by chronic infections, such as rhinoscleroma, syphilis, leprosy, and lupus, or by excessive surgical excision of the inferior turbinates or the nasal septum, with the occurrence of "empty nose syndrome" [11, 12].

10.3 Treatment

The aims of treatment in case of atrophic rhinitis are to eliminate the incriminating factors, to moisture the nasal mucosa, to clear the nasal crusts, and to improve the functionality of the mucosa of the nose and paranasal sinuses [13]. Specifically, the two main objectives are to restore the mucosal hydration and to minimize the crusting. The treatment should be individualized, according to the disease etiology.

In order to improve the symptoms of these patients, multiple therapeutic methods have been proposed: topical drugs, systemic therapies, and surgical techniques.

For iatrogenic atrophic rhinitis, the most important step is the prevention and limitation of the excessive removal of the nasal turbinates or the septum. In case of systemic diseases that determine the atrophy of the nasal mucosa, the specific systemic treatment must be initiated by the specialists, taking into consideration the severity, to prevent the irreversible destruction of the rhinosinusal mucosa and bony structures, in order to minimize the progressive and irreversible destruction of sinonasal structures.

The therapeutic classes include antibiotics, for example, in case of tuberculosis; systemic glucocorticosteroids (in case of Wegener's granulomatosis or sarcoidosis); and immunosuppressive agents, cyclophosphamide, methotrexate, infliximab, or azathioprine, as an adjunct treatment for systemic diseases.

Symptomatic approach for atrophic rhinitis includes several methods, such as nasal lavage, local ointments, topical or systemic antibiotics, crusts removal, and eliminating the promoting factors for the mucosal atrophy.

The most important step in the treatment of atrophic rhinitis is the nasal irrigation, both to eliminate the crusts and to prevent the dryness of the nasal mucosa. In order to make this treatment efficient, the irrigation should be performed several times per day [14–16].

Despite the existence of various therapies, the results are still not satisfying and the appropriate treatment is not established yet, therefore it is often empirical [1, 17]. From the patient's point of view, it is difficult to follow the treatment for a long period, with slightly symptomatic improvement, in most cases.

There are several types of irrigations and therapeutic classes available, which are to be detailed below.

10.3.1 Nasal Irrigations

The most frequently used solution is an equal combination of sodium bicarbonate and sodium diborate, which has an antiseptic and bactericidal effect, and sodium chloride, which makes this solution isotonic. This substance is recommended to be

used between 3 and 6 weeks, and the assessment of the nasal symptoms revealed that it determined a significant subjective improvement. The use of this solution is best accompanied by the endoscopic removal of the nasal crusts and secretions.

A clinical study investigated the role of isotonic sodium chloride solution, compared to pure sesame oil, in the treatment of the patients with atrophic rhinitis, and the results indicated better subjective outcome when both substances were associated, and the sesame oil alone was statistically more effective than isotonic sodium chloride solution alone [18].

10.3.2 Dexpanthenol

A clinical study performed by Kehrl in 1998 [19] investigated the efficacy of Dexpanthenol spray, in a saline product, for patients with atrophic rhinitis. The results indicated that dexpanthenol was efficient, but did not prove superior efficacy statistically significant in these patients, compared to placebo. The spray was well tolerated, the therapeutic compliance was good, and the results were confirmed by the findings in anterior rhinoscopy and nasal endoscopy.

10.3.3 Glycerine Nasal Drops

Glucose, in high concentration (25%), has the ability to inhibit the saprophytic bacteria, by producing lactic acid, with an acid pH, and the subsequent inhibition of the bacterial growth. Also, it stimulates the development of commensal bacteria. Glycerine is a nonvolatile alcohol, with hygroscopic properties, which has been found to have antiinflammatory capacities and to stimulate cell maturation. In case of atrophic rhinitis, it absorbs water and reduces the nasal crusts. Glycerine can also be local irritant and it stimulates the vasodilation inside the nasal mucosa.

10.3.4 Placental Extract Injections

Placental extracts have been proven to have biogenic, mitogenic, and angiogenic properties, and their use in the treatment of atrophic rhinitis is based on their characteristics. Injections with placental extracts inside the nasal mucosa may have the effect of narrowing the nasal fossae and to stimulate vasodilatation. Unfortunately, their effects usually disappear in approximately 8 weeks after the treatment [13].

A clinical randomized control study compared the efficacy of submucosal injection of placentrex and oral antibiotic therapy with rifampicin, in patients with atrophic rhinitis. The assessment consisted in subjective and objective evaluation of the symptomatology, as well as the modifications in histopathology findings. The study indicated that the patients treated with rifampicin proved better results, compared to patients who underwent submucosal injections with placentrex [13].

Acetylcholine was used in topical products, based on its vasodilatory effect, with improvement of the seromucous glands activity.

Vitamins and oligoelements were administered in patients with malnutrition and vitamin deficiency.

Vaccines for the bacterial infections promoting atrophic rhinitis were proposed, such as *Bordetella bronchiseptica*, but further clinical study on humans are needed, in order to prove their possible role and efficacy in the management of this disease.

10.3.5 Antibiotics

Nasal irrigations can be used in conjunction with systemic or topical therapies, in patients with atrophic rhinitis. The most frequent systemic therapy is represented by antibiotics. Antibiotics are used to treat nasal infection and the purulent secretions that originate under the crusts, but they are not recommended on long term, being ceased and replaced with nasal irrigations [20]. It is recommended for the antibiotics to be administered only after obtaining a bacterial and fungal culture from the nasal fossae. There are several classes available, related to the bacterial etiologic agent, which can have topical or systemic forms of administration.

In the past years, the use of local chloramphenicol and streptomycin proved good therapeutic results. Taking into consideration that the most frequent bacterial causative agent is *Klebsiella ozaenae*, it is reasonable and efficient to use systemic aminoglycosides, such as tobramycin, for 14 days, together with intranasal gentamicin. Also, good results were noticed when clinicians indicated rifampicin 600 mg per day, for 3 months.

Recently, fluoroquinolones, especially ciprofloxacin, in a daily dose of 500–750 mg, for a duration between 1 month and 3 months, have proven clinical efficacy, in terms of reducing the nasal crusts and the smell; also, bacterial inhibition of *Klebsiella ozaenae* was demonstrated [20]. The patients were followed for 26–74 months after treatment, and researchers reported disappearance of the specific smell, the nasal crusts, and absence of *Klebsiella*. Currently, ciprofloxacin in oral use remains one of the most suitable therapies for the treatment of atrophic rhinitis.

10.3.6 Alternative Therapies

Besides standard approaches, with eliminating the predisposing factors, nasal irrigations and systemic antibiotics, several alternative methods have been proposed in the last years, due to the fact that the results are still unsatisfactory.

10.3.6.1 Submucosal Infiltrations of Polimethacrylate

A new treatment was tried in atrophic rhinitis, with submucosal infiltration of polimethacrylate. Local infiltration of Metacrill determined a reduction of nasal crusting and the smell in patients with atrophic rhinitis or ozena. The patients also reported significant clinical improvement, with diminished nasal fetidness [21]. Metacrill is largely used in the treatment of face lift because this substance improves the face contours, diminishes wrinkles [22]. But still, more studies must be made, to establish the exact role of Metacrill and its appliance in atrophic rhinitis.

10.3.6.2 Ozone

Ozone is a form of alternative therapy in medicine due to its mechanisms of action: bacterial and fungal inactivation, stimulation of the oxygen metabolism, angiogenesis, fibroblasts activity, and enhancing the normal immune system. A study performed on albino male rats, with induced atrophic rhinitis by administering *Pasteurella multocida* toxin diluted, investigated the role of ozone in regenerating the cells. They noted that there was no significant difference between the groups regarding the histopathologic findings, and they concluded that ozone administration has very limited or no effect at all in case of atrophic rhinitis [23, 24].

10.3.6.3 Prosthesis

In cases refractory to medical therapy, nonsurgical techniques have been described for closure of the nasal vestibules [25–28], using different types of prosthesis, made from a material called dimethylpolysiloxane or from an acrylic resin. Another type of prosthesis for nasal closure is an obturator, realized using the classical ear mold methods. Patients can wear these prostheses, with minimal cosmetic implication, allowing, at the same time, access for the examination and cleaning of the nasal fossae.

10.3.6.4 Stellate Ganglion Injections

In the past years, stellate ganglion injections to block its activity were also tried because it was noticed that, in case of ganglion inhibition, nasal congestion and secretions appeared [29, 30]. This technique is not currently used and it needs more clinical study to establish its efficacy.

10.3.6.5 Tocopherol Acetate

Several researchers have postulated the important role of vitamin E (alpha-tocopheryl acetate) for its effects: antiinflammatory, antioxidants, immunostimulants, stabilizing the cell membrane, and promoting the skin barrier function. A clinical study performed on patients with atrophic rhinitis evaluated the effects of topic vitamin E, based on subjective and objective assessment. All the patients included in the study showed an improvement of the nasal dryness sensation and increased inspiratory nasal flow [31, 32]. The rhinomanometric assessment confirmed the increase of the nasal airflow, and nasal endoscopy showed a significant reduction of the nasal crusts and an increase of the nasal mucosa hydration.

Alternatives presented in the literature are the following: autologous platelet-rich plasma, use of subcutaneous adipose tissue, cancellous bone, grafts of placenta, or autologous bone marrow.

Despite the correct maximal medical treatment, the majority of the patients will have nasal crusting and disease relapses, every time the therapy is ceased. In case of failure of medical therapies, various surgical techniques have been proposed. Surgery is indicated for reduction of the nasal cavity dimensions and to prevent excessive dryness of the nasal mucosa. Many techniques and materials have been proposed, but the results are mostly heterogeneous [16, 33].

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11 Surgical Treatment of Empty Nose Syndrome: Inferior Turbinate Reconstruction Using Intranasal Mucosal Flaps

Stefano Di Girolamo, Mariapia Guerrieri, Barbara Flora, and Francesco Maria Passali

Abbreviations

ENS	Empty nose syndrome
ENS6Q	Empty nose syndrome 6-item questionnaire
IMAP	Inferior meatus augmentation procedure
IT	Inferior turbinate
SNOT-25	Sinonasal obstruction test-25

11.1 Background

Empty nose syndrome (ENS) commonly refers to a rare post-surgical disorder associated with symptoms that arise from iatrogenic nasal tissue loss, mostly involving the inferior turbinates [1].

Patients suffering from ENS usually complain about a paradoxical sensation of nasal obstruction, despite objectively wide, patent nasal fossae; nasal crusting; dryness or excessive nasal discharge; headache; dyspnoea and a sense of suffocation [2, 3].

ENS symptom severity ultimately affects the quality of life of these patients, causing a significative impairment in activities of daily living [4].

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Little is known about the aetiology of the ENS, but it must be considered as a multifactorial physiopathological mechanism involving structural changes of nasal resistance, poor mucosal wound healing, reduced nasal air conditioning and decreased sensory input [5].

Alterations in normal airflow due to excessive turbinate resection and the loss of neural sensitivity are suspected as key contributing factors in the genesis of ENS [2].

The loss of the turbinates, namely the inferior ones, in facts, leads to an alteration of the meatal structures, causing turbulent, less efficient airflow [6], as confirmed at computational fluid dynamics (CFD) studies [2].

Moreover, the inferior turbinates host the higher trigeminal sensitivity in the nasal mucosa [7]and are believed to provide somatosensory and chemosensory perceptions, which result in the feeling of patency of the nasal fossae [8]. Therefore, a near-total resection of inferior turbinates may reduce critically the absolute number of these trigeminal receptors, contributing to the paradoxical feeling of obstruction that affects ENS patients [5].

The loss of turbinate tissue ultimately leads to the alteration of nasal physiology, decreasing the ability of nasal mucosa to humidify and heat the inspired air, affecting the mucociliary clearance and the IgA secretion rates, eventually producing crusts that further impair the sensation of airflow [3, 9].

Given the very limited options ENS patients have once the symptoms are manifest and the diagnosis is clear, prevention is essential and any unnecessary intranasal surgery should be avoided [1].

When it comes to treatment, the first approach in these patients is the medical management, which consists in mucosal moisturizing, hydration with saline or oil-based lubricants, increased fluid intake and an aggressive regimen of nasal saline irrigations [10].

In the last decades, surgical treatment has gained a key role in the management of ENS patients.

11.2 Surgical Treatment

Concerning the surgical treatment of the ENS, it has proved to be a safe and effective alternative, especially for those patients who cannot get any relief from medical treatment. Its purpose is to reduce the nasal cavity volume, to increase the nasal airway resistance and to rebuild the nasal anatomical structures [11].

Nowadays, surgical interventions involve the use of submucosal implants to reconstruct the contour of the nasal cavity, and they have been demonstrated to improve patients' rhinological and psychological symptoms [12].

Lee et al. investigated the impact of site of implantation, and they assessed that the lateral nasal wall was associated with a greater improvement of symptoms (SNOT-22) rather than the nasal floor [13].

The reconstruction of the inferior turbinate on the lateral nasal wall, in fact, narrows the inferior meatus, increasing the velocity of the airflow and the wall shear

stress during inspiration, eventually leading to a more physiological pattern of airflow and, therefore, to a better outcome [14].

Analysing literature, many different materials have been used during the years with the purpose to treat ENS symptoms, starting from intranasal submucosal fillers like hyaluronic acid gel [15] or carboxymethylcellulose/glycerin gel [16], which provide a considerable yet transient improvement of symptoms. Other surgeons prefer to inject in vitro expanded autologous adipose-derived stem cells [17] or autologous stromal vascular fraction extracted from abdominal fat and diluted [18].

Good results have been registered also using acellular dermal (alloderm) grafts [19], Medpor [20, 21], beta-tricalcium phosphate [22] or hydroxyapatite cement [23].

Autologous cartilage has indeed obtained long-lasting results [24]: costal cartilage or conchal ones are the most used [25].

We present here our experience on ten patients who were treated with a new technique to create a 3D reconstruction of the inferior turbinates, combining the use of autologous cartilage with the preparation of an endoscopic-assisted intranasal mucosal flap.

11.2.1 Pre-operative Evaluation

The pre-operative evaluation of patients with a history of nasal surgery comprehends the administration of subjective questionnaires (SNOT-25 [26] and ENS6Q [27]), which investigate the sensation of nasal congestion, nasal burning, nasal dryness or excessive discharge, hyposmia, epistaxis, dyspnoea, and sense of suffocation.

Nasal endoscopy evaluates the patency of the nasal fossae and the absence of the inferior turbinates.

CT scan better explores the post-surgical anatomy of the nasal fossae (Fig. 11.1). It also very often reveals a chronic inflammation and congestion of the paranasal sinuses, which is a further mark of sinonasal dysfunction that contributes to worsen the burden of symptoms affecting patients' quality of life.

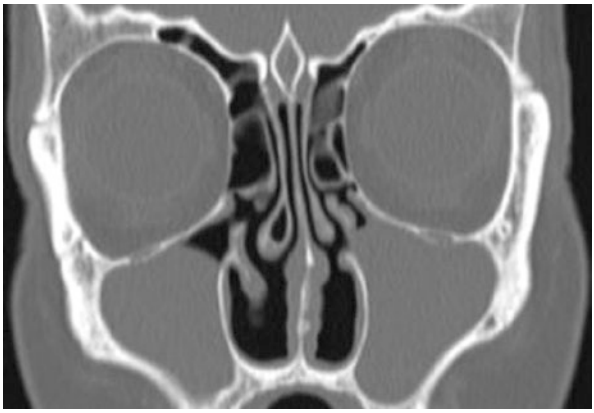

Fig. 11.1 Pre-operative CT scan shows the absence of the inferior turbinates. It is also possible to appreciate the sinusitis that often afflicts ENS patients, worsening their symptoms

11.2.2 Surgical Technique

After general anaesthesia is induced, a 0° rhinoscope is used to explore the nasal fossa, where the lack of the inferior turbinate might be recognised and quantified as total or near-total (only parts of the turbinate are left, such as the head or the tail) (Fig. 11.2). Several key landmarks might be identified at this moment: nasal septum, Hasner's valve, middle turbinate and middle meatus, superior turbinate and superior meatus.

A fine needle is used to inject a solution of Carbocaine 1% + Adrenaline 1:100,000 in the submucosa of the nasal floor and of the lateral nasal wall, to prevent excessive bleeding. Concerning this particular matter, it is also important that the anaesthesiologist keeps the patient's blood pressure as low as possible.

A graft of autologous cartilage must be drawn from the nasal septum, or alternatively from the auricular concha. It is hence remodelled in a thin stripe.

A paraseptal incision of the mucosa of the nasal floor, from back to front, parallel to the nasal septum is thereafter performed using a falciform surgical knife (Fig. 11.3a).

A mucosal flap is then created, carefully detaching the mucosa of the nasal floor all the way to the lateral nasal wall (Fig. 11.3b), preserving its vascular supply, provided by an inferior branch of the sphenopalatine artery.

The mucosal flap is hence shifted and rolled toward the lateral nasal wall (Fig. 11.3c), where the inferior turbinate should have been, and sutured to it in its most posterior part, using a Vicryl 3-0 rapid wire, in order to create a pocket to keep the graft in its place.

Fig. 11.2 The pre-operative endoscopy shows an empty left nasal fossa, where the inferior turbinate is completely absent. The valve of Hasner is evidenced with a curved aspirator

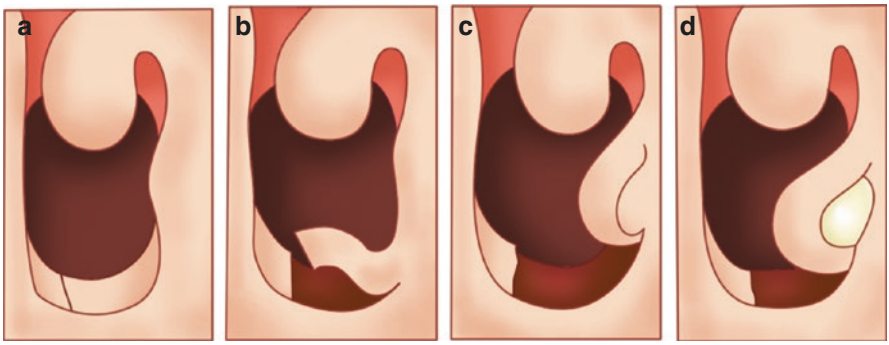

Fig. 11.3 (**a**) Incision of the mucosa of the nasal floor; (**b**) creation of the mucosal flap; (**c**) the flap is shifted and sutured to the lateral nasal wall; and (**d**) insertion of the cartilaginous graft underneath the mucosal pocket

The autologous cartilaginous graft is therefore inserted underneath the mucosal flap on the lateral nasal wall, recreating a three-dimensional structure of a neo-inferior turbinate (Fig. 11.3d). A piece of haemostatic sponge is then placed beneath the neo-turbinate, to prevent its dislocation.

11.2.3 Post-operative Care

Patients are dismissed from the hospital the day after the procedure. Post-operative controls are usually scheduled after 1 week and 1 month from the operation. Post-operative endoscopy is regularly used to evaluate the results of the inferior turbinate reconstruction and mainly to make sure that the cartilaginous graft remains in place and the mucosa heals normally (Fig. 11.4).

Subjective questionnaires like ENS6Q and SNOT-25 are administrated again on every post-surgical control, in order to quantify the betterment of patients' quality of life. There is evidence that this kind of surgery eventually produces a consistent and durable improvement of ENS symptoms.

Nasal irrigation and oil-based lubrication of the nasal fossae are usually recommended to the patient, once the mucosa has completely healed.

11.2.4 Post-operative Complications

Post-operative complications are rare following this kind of endoscopic nasal surgery. Some more common complications include, but are not limited to: epistasis, infections, epiphora due to the obstruction of the valve of Hasner, dislocation of the graft or its reabsorption, and persistence of the symptoms. Concerning the cartilage donor site, it usually heals quickly, without any further symptom for the patient. Even the mucosa of the nasal floor re-epithelizes completely.

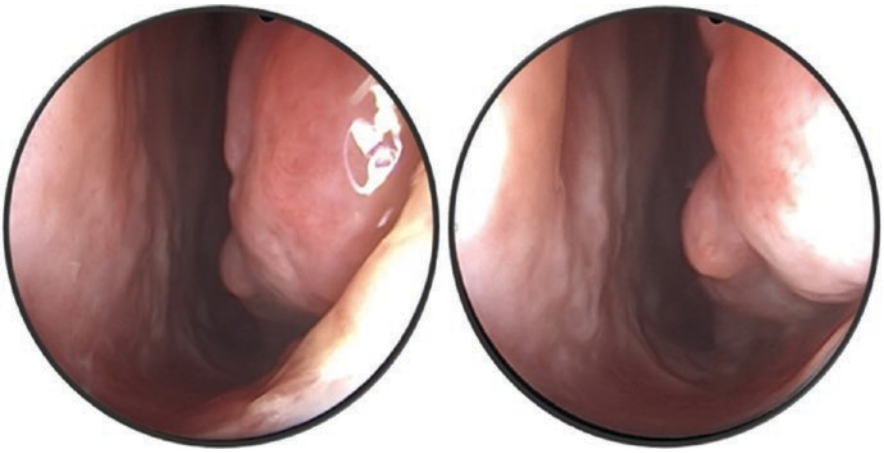

Fig. 11.4 The 1-month post-operative endoscopy shows the neo-turbinate covered by healthy mucosa, which has also re-epithelised the floor of the nasal fossa

11.3 Conclusion

The inferior meatus augmentation procedures (IMAP) have shown to improve the quality of life of ENS patients, regarding both ENS specific symptoms and psychological well-being [28].

The new technique discussed here, the 3D reconstruction of the inferior turbinate using an intranasal mucosal flap combined with an autologous cartilage graft, represents a valuable alternative in the treatment of ENS patients, since it is easy to perform; it uses autologous grafts which are perfectly tolerated from the patient and it does not change the aesthetic of the face.

It can also be combined to the functional endoscopic sinus surgery, when needed, so to treat at the same time both the symptoms caused by the dysventilation of the paranasal sinuses and those related directly to the empty nose syndrome (Fig. 11.5). The improvement of these symptoms is quite rapid and stable after 6 months from the operation, with a considerable reduction of the ENS6Q and SNOT-25 scores.

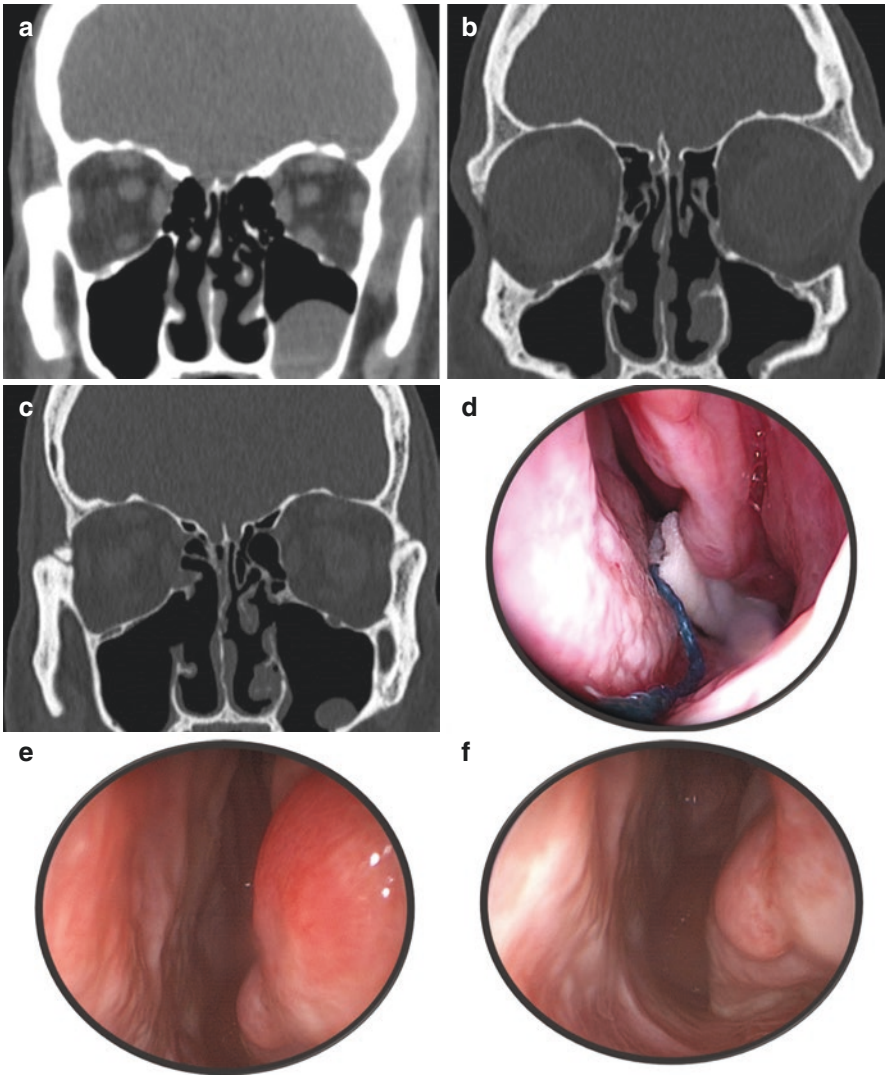

Fig. 11.5 A patient who had undergone three different nasal surgeries presented with sinusitis and absence of the inferior turbinates. He underwent FESS (only on the right side) combined with the endoscopic reconstruction of the left inferior turbinate, with a significant improvement of his symptoms. (**a**) Pre-operative CT scan shows that the inferior turbinates are absent. (**d**) Pre-operative endoscopy of the left nasal fossa shows the near-total absence of the inferior turbinate. (**b**, **c**) Six months post-operative CT scan shows the successful reconstruction of the left inferior turbinate, with a reduction of the maxillary sinus inflammation. (**e**, **f**) At the 6 months post-operative endoscopy the neo-turbinate appears well trophic, covered with healthy mucosa

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Surgical Treatment of Atrophic Rhinitis: Inferior Turbinate Augmentation with Submucosal Injections

12

Valerio Cervelli and Gabriele Storti

Abbreviations

ADSCs	Adipose-derived stromal/stem cells
AR	Atrophic rhinitis
BM-MSCs	Bone marrow-derived mesenchymal stem cells
ECM	Extravascular matrix
ENS6Q	Empty nose syndrome 6-item questionnaire
GFs	Growth factors
GMP	Good manufacturing practice
HA	Hyaluronic acid
HPE	Human placental extract
MSCs	Mesenchymal stem cells
PRL	Platelet-rich lipotransfer
PRP	Platelet-rich plasma
SNOT	Sino-nasal outcome test
SVF	Stromal vascular fraction

12.1 Introduction

Atrophic rhinitis does not have a well-defined etiology in primary form but could have multiple etiologies in secondary forms, with similar clinical presentation. Therefore, multiple therapies have been proposed ranging from local therapies to surgical interventions, including autologous cartilage grafts and allografts.

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Nonetheless, some elements are common in both the primary forms and the various described secondary forms, including the so-called *empty nose syndrome (ENS)*. The most significant pathological features involve the mucosa and the mucociliary clearance, and the inferior turbinates, with a volume reduction.

In particular, in the primary form of atrophic rhinitis, the mucosal changes have a cardinal role. There is a progressive loss of goblet mucinous cells and cilia, with abundant inflammatory infiltrates, which ultimately leads to the disfunction of the mucociliary clearance. The mucos stasis causes mucosal dehydration, atrophy, and crusting. Parallelly, a form of vasculitis of the submucosal vessels reduces the regeneration of the mucosal epithelium and weakens its barrier against pathogenic bacterial agents, which superinfect the crusts, causing the typical foul smell. The chronic inflammatory process determines, in the most severe cases, progressive resorption of the boney structure of the turbinates and further impairment of the nasal air conditioning system with enlargement of the nasal cavities.

On the other hand, in some forms of secondary atrophic rhinitis, like the ENS, the first driver of mucosal atrophy is an unphysiological airflow due to a reduced turbinates' volume and a lowered nasal airway resistance, with an enlarged nasal cavity.

Altered airflow reduces the mucus production from the goblet cells and causes a dry nose sensation and crusting in these patients. The lowered nasal airway resistance, the unphysiological flow, the reduced contact between air and mucosa, and the loss of function of the mucosal cells cause the phenomenon called paradoxical obstruction, which impairs substantially the quality of life of the patients affected. Even though the nasal cavities result enlarged, the patients experience a sense of drastic reduction of the air inflow with a subjective sense of difficult nasal breathing and progressive and chronic development of psychological symptoms like anxiety and depression.

At a later stage, primary and secondary atrophic rhinitis and ENS have many overlapping features, including mucosal atrophy and volume reduction of the boney turbinates.

Usually, treatments for primary and secondary forms of atrophic rhinitis range widely from conservative treatments, consisting of mucosa humidification, nasal irrigations, liquid paraffin, antibiotics, and antimicrobials, to surgery intended to restore an ideal airflow in the nasal cavities.

Submucosal injections are therapies which aim to have long-lasting benefits, compared to conservative treatments and to be less invasive than surgical procedures. Furthermore, depending on the injected compound, they can have different effects, either a volumizing effect on the turbinates or a regenerative effect on the mucosa or both.

The discovery of the regenerative potential of the adipose-derived stromal/stem cells (ADSCs), contained in the stromal vascular fraction (SVF) and isolated from the adipose tissue, offered the possibility to have a bioactive filler which can induce cellular regeneration, neoangiogenesis and it can also differentiate into mucosal

cells. Moreover, they show a significant immunomodulatory capacity, which can reduce chronic inflammation. Therefore, the SVF derived from the adipose tissue has been investigated not only for volume filling but also for an active repair of the mucosal areas, which the atrophic process damaged.

The platelet-rich plasma (PRP) has been described in these years as a readily available and ready-to-use source of growth factors (GFs). The GFs contained in the platelets' granules can stimulate a vasculogenic response to modulate the cellular chemotaxis and the immune response. Furthermore, they are also a potent inducer of cellular proliferation. For these reasons, PRP has also been tested as a possible therapeutic tool for atrophic rhinitis, to invert the mucosal atrophy.

The human placental extract (HPE) proved in many conditions, like radiotherapy-induced oral mucositis and oral submucosal fibrosis, its efficacy in the promotion of wound healing and immune modulation. It has been tested for this reason for the treatment of AR to restore a proper mucosal trophism.

In AR forms where the reduction of the turbinate volume and the enlargement of the nasal cavities have a pivotal role, like the ENS, the submucosal injection of resorbable filler like hyaluronic acid (HA) and carboxymethylcellulose/glycerin gel have been attempted. The use of these molecules aimed to provide relief, although temporary, from the subjective symptoms caused by the paradoxical obstruction, thus avoiding more invasive surgical procedures.

In this chapter, we are going to review the different pharmacological and cellular therapy used for submucosal injections to increase the turbinate volume and to reverse the atrophic changes in the mucosal epithelium. In Fig. 12.1, the different properties of the different products used for submucosal injection are schematized in terms of volume filling and regenerative properties.

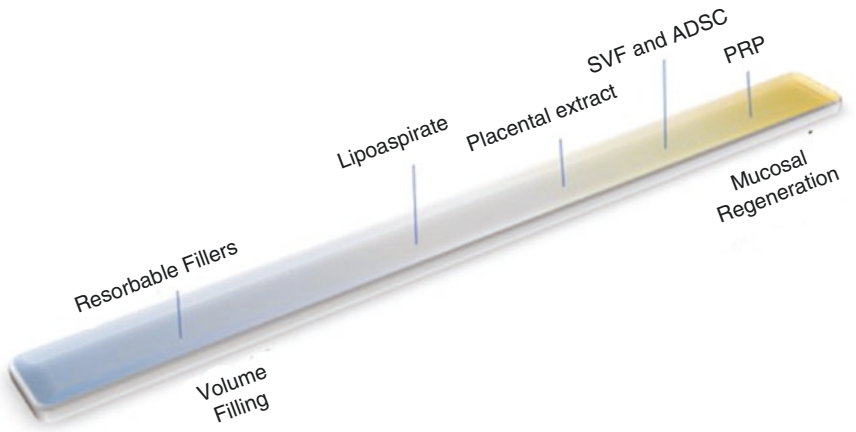

Fig. 12.1 Different products for submucosal injections have different intensity of various effects which range from the volume filling to the mucosal regeneration

12.1.1 Adipose-Derived Stromal/Stem Cells (ADSCs) and Stromal Vascular Fraction (SVF)

In 1966, Friedstein isolated for the first time, from the bone marrow, a cellular population with staminal characteristics, which differed from the hematopoietic stem cells. He defined this population as *mesenchymal stem cells (MSCs)*. They were characterized according to specific features they showed when cultured in vitro. In particular, they can adhere to plastic in standard culture conditions, show distinct surface markers, and can undergo trilinear differentiation (adipogenic, osteogenic, and chondrogenic differentiation). Specific surface markers were identified and included in the classification. MSCs are positive for CD13, CD29/ITGB1, CD44, CD73, CD90, CD105, and CD106/VCAM-1 and typically lack surface proteins like CD31/PECAM-1, CD34, CD45/LCA, and CD116.

The first population of MSCs was described in the bone marrow, but over the years, similar cells were found in several other tissues, including cord blood, peripheral blood, skeletal muscle, dermis, synovial membrane, and adipose tissue.

In 2001, Zuk and colleagues discovered a population of MSCs in the adipose tissue, which went under the name of *adipose-derived stem cells (ADSCs)*. This cell population was isolated through enzymatic digestion from the lipoaspirate. These cells, which are located in the perivascular niche, were later on phenotypically characterized and described.

According to the joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and of the International Society for Cellular Therapy (ISCT), the ADSCs were immunophenotypically defined as positive for CD13, CD29, CD44, CD73, CD90, and CD105, while they were negative for CD31 and CD45. Furthermore, they should be able to adhere to plastic and proliferate in vitro and to undergo trilinear differentiation (adipogenic, chondrogenic, and osteogenic) as the other MSCs.

The discovery of the ADSCs and the possibility to isolate them from the lipoaspirate paved the way for great possibilities in the field of regenerative medicine. Compared to the BM-MSCs and other sources of MSCs, the ADSCs could offer several advantages. First of all, the adipose tissue is easy to harvest, even in relevant quantities, with minimal discomfort for the patients. Moreover, it has been described that the amount of MSCs attainable from the adipose tissue is up to 1000-fold higher than the bone marrow, thus allowing a more straightforward use in clinical practice without the need for previous in vitro expansion. When in vitro, ADSCs proved to have a longer lifespan, a shorter doubling time, a higher proliferative capacity, and reduced senescence compared to BM-MSCs.

The ADSCs are located in the perivascular niche together with other cell types. All together, they are part of the so-called *stromal vascular fraction (SVF)*. The SVF is a heterogeneous mix of different cell types, which include, besides the ADSCs, macrophages, vascular endothelial cells, smooth muscle cells, fibroblasts, and pericytes. The SVF is embedded into the extracellular matrix (ECM), which constitutes a support network and strictly regulates their interplay [1].

In order to obtain the SVF for clinical use, it is necessary to dissociate it from the surrounding ECM. The first method described was the enzymatic digestion through the use of collagenase. The purified fat, after the removal of infiltration fluid and oil, was processed with 0.1% of bovine collagenase for 45 min at 37 °C. This allowed digesting the ECM completely and releasing the SVF with an optimal cell yield for clinical use. The enzymatic method for SVF isolation from the lipoaspirate has been used and exploited in several commercial kits. Among its main pros, there is an optimal cell selection and yield, which usually does not require cell expansion. Nonetheless, the process is expensive and time-consuming, which prolongs the surgery time when used intraoperatively.

Furthermore, in the European Union, the European Medicines Agency (EMA) classifies the enzymatic separation of the SVF as a substantial manipulation which requires the use of Good Manufacturing Practice (GMP) facilities, which raised the cost of the procedure and made it difficult to apply to everyday clinical practice.

In order to overcome this critical limitation, methods for mechanical separation of the SVF have been described. Mechanical methods for the SVF separation exploit several physical forces, including vibrational energy, mincing, mechanical crushing, aggressive centrifugation, vortexing, and ultrasound cavitation.

The mechanical separation is cheaper and faster, making it easier to use it in intraoperative situations. Nonetheless, the main drawback is the high cell dispersion with lower cell yield. This limitation implies the use of a more considerable amount of lipoaspirate.

The SVF is a product containing cell types other than ADSCs. It is also possible to culture the SVF and to expand the ADSC population. These processes allow having an injectable product constituted only by MSCs, which maximizes the cellular quantity and its effect, while reducing the volume to inject.

Even though in a randomized trial, the efficacy of the injection of ADSCs alone revealed superior to the injection of fat, this therapeutic option is quite far away from being available in everyday practice. The use of expanded ADSCs is time-consuming and two separate procedures are needed, one for the harvesting and a second one for the reinjection. Furthermore, it is expensive and requires GMP facilities, which are not available in smaller centers.

Last but not least, the use of purified lipoaspirate, containing the ADSCs, could also be considered as a potential filler for the inferior turbinate. Several methods to purify the adipose tissue have been described, but the most standardized is the one introduced by Coleman and colleagues. The lipoaspirate is processed through centrifugation at 3000 rpm for 3 min. In the centrifugated fat, three layers are visible:

- An upper layer containing the oil, which results from broken adipocytes
- A middle layer containing the purified lipoaspirate
- A lower layer containing the infiltration fluid, and red blood cells (RBCs)

Injecting the resulting fat parcels is a faster and cheaper method, which also allows having a relevant effect of volume filling. Nonetheless, the main drawbacks

for the use of the purified lipoaspirate are its variable degree of resorption, which often requires multiple procedures, and the limited amount of ADSCs contained in the volume, which lowers its regenerative effects compared to other products like SVF or expanded ADSCs.

The use of the purified adipose tissue, of the SVF or expanded ADSCs for the treatment of primary and secondary forms of atrophic rhinitis, including the ENS, has a significative biological rationale behind it. These cells have multiple effects on the recipient site, which could relieve the nasal symptoms and the mucosal atrophy.

In particular, besides the immediate volume effect, the cellular component of these products proved to be efficacious in stimulating angiogenesis, immunomodulation, and tissue regeneration.

The ADSCs are cells with a high paracrine secretory activity. They can secrete significant amounts of numerous *growth factors (GF)*, which have several effects, including stimulation of vascular growth, cell proliferation and differentiation, and regulation of the immune response. The GFs involved in these processes are mainly the VEGF, which is a potent inductor of angiogenesis that stimulates the migration of vascular endothelial cells, and the TGF-β, which regulates the immune response of the lymphocytic and the macrophagic population. Under the stimulus of the TGF-β, macrophages undergo a shift from the pro-inflammatory M1 phenotype toward the pro-reparative M2 phenotype, which lowers the pro-inflammatory response, has an anti-apoptotic effect and promotes the angiogenesis and the lymphangiogenesis [2].

The effect of the ADSCs is not only paracrine but also directly generated via cellular differentiation. As mentioned above, the ADSCs have multiple differentiative capacities, which include the possibility to differentiate into adipocytes, chondrocyte, osteoblasts, and vascular endothelial cells. It has been demonstrated that the ADSCs can differentiate into mucosal epithelial cells in vitro. Under the stimulation of the EGF, they acquire the typical epithelial polygonal/rounded shape and proliferate organizing in an adherent monolayer, with clusters showing a characteristic cobblestone pattern. Furthermore, they express different cytokeratins, including cytokeratin-7, cytokeratin-14, and cytokeratin-19, which are typical of epithelial-like cells and are not expressed by undifferentiated ADSCs.

In animal models of atrophic rhinitis, it has been histologically highlighted that the submucosal injection of fat tissue was able to reduce glandular atrophy in the submucosa. In contrast, it had a limited effect on inflammatory infiltrate, squamous metaplasia, and keratinization of the superficial epithelium and vascular proliferation [3].

The data on human studies are conflicting. Different solutions were tested, which involved different products derived from the adipose tissue, including lipoaspirate with or without PRP, expanded ADSC with or without lipoaspirate, and autologous SVF.

Most of the studies focused on the ENS, a few on primary atrophic rhinitis.

The lipoaspirate was evaluated in combination with the PRP to treat primary atrophic rhinitis [4]. The adipose tissue was purified according to Coleman's technique and then mixed with PRP, in order to reduce its resorption rate. Adding 0.5 ml

of PRP per each ml of adipose tissue demonstrated a significant improvement in the graft take rate. The high load of GFs contained in the PRP mediates this effect.

The injection of an average of 3 ml per nostril of lipoaspirate mixed with PRP was able to regenerate a healthy mucosa, with the total disappearance of the crusting, and no signs of atrophy, after 6 months. The nasal mucociliary clearance time result significantly reduced and the subjective symptoms were improved as well. Nonetheless, the total volume of the nasal cavity did not change significantly.

Similarly, other authors tried to enrich the lipoaspirate with ADSCs in order to increase its regenerative potential and to boost the graft survival [5]. The procedure was well tolerated without major complications. Both the adipose tissue alone and the adipose tissue mixed with 5 ml of expanded ADSCs per each nostril were able to improve the subjective symptoms and to reduce the nasal crusts. After 6 months, the group treated with the ADSC-enriched fat had a complete re-epithelization of the nasal mucosa and a reduction of the inflammatory infiltrate, which was not visible in the patients treated with lipoaspirate only. Furthermore, ADSC-enriched fat determined an increased expression of several genes involved in the mucus secretion. These results were confirmed for up to 6 months.

Another treatment option to exploit both the regenerative features of the ADSCs and the volumizing effect of fat is to use the expanded ADSC in combination with fat particles [6]. The submucosal positioning of adipose graft had, as one of the main drawbacks, the high chance of resorption. The addition of ADSCs' injection intended to improve the vascularization of the graft and increase its chance to survive. Furthermore, the high quantity of GFs secreted by the ADSCs could favor cell proliferation and mucosal re-epithelization. The use in the ENS of this approach, with ADSC and fat particles from abdominal fat, demonstrated a significant improvement in the nasal obstruction and the nasal mucociliary clearance, with the relief of the subjective symptoms and of nasal crusting as well. At the rhinomanometry, the nasal volume and the minimum cross-sectional areas significantly decreased, while the nasal resistance increased. These improvements remained stable up to 9 months after treatment. An increase of caliciform cells and the reduction of the inflammatory infiltrate were also histologically observed.

The injection of the SVF derived from the abdominal fat was also tested [7]. The SVF was able to reduce the inflammatory markers in the ENS, given its immunomodulating properties. It decreased the level of expressions of IL-1β and IL-8, after the injection, compared to the baseline. Nonetheless, the injection of the SVF did not significantly associate with an improvement in the symptoms and patient satisfaction.

Considered altogether, the injection of adipose tissue with or without its derivatives, like the SVF and expanded ADSCs, is a promising treatment for the different forms of atrophic rhinitis. They revealed a significant efficacy in symptoms' reduction, inflammation control, and reversal of mucosal atrophy and crusting. Nonetheless, numerous limitations are present. First of all, the quality of the evidence supporting these procedures is low. Mostly single-center observational studies are available, without a control group and with a low number of patients and a short follow-up time.

Moreover, many of these treatments, especially those involving the use of expanded ADSCs, are expensive and undergo severe regulatory issues in many countries, which complicate their use in everyday clinical practice, as mentioned above.

Therefore, even though attractive, these treatment protocols need further validations before entering as a standard of care in the atrophic rhinitis.

12.1.2 Platelet-Rich Plasma (PRP)

Platelets are one of the most abundant storage for GFs. Different GFs are present in the α-granules, which are released from the platelets when the activation cascade initiates. *Platelet-rich plasma (PRP)* is a blood derivative for autologous use. It is obtained by centrifugation of the whole blood and increasing concentration of the platelet number.

Several protocols and commercial kits were elaborated to obtain the PRP. The methods differ mainly in the centrifugation speed and the use of one or two centrifugation steps. Another passage that could differ among various PRP preparation methods is the activation. The activation, usually through calcium chloride or thrombin, triggers platelet degranulation and the consequent release of the GFs that platelet granules contain.

These GFs control cell survival, proliferation, and regenerative processes, in general. Among the most relevant GFs, we can find the platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor (IGF).

The VEGF is one of the most prominent promoters of neoangiogenesis, which can recruit and induce the proliferation of vascular endothelial cells. It also regulates collagen synthesis.

The bFGF cooperates in the neoangiogenesis through the stimulation of the sprout of new vessels from the existing ones. It regulates the activity of MSCs, fibroblasts, and endothelial cells.

The TGF-β is a potent regulator of collagen synthesis, as well. Furthermore, it plays a crucial role in the induction of the proliferation of MSCs, and it is one of the most pivotal players in the local immunomodulation. The TGF-β can regulate the local microenvironment, acting on lymphocytes and macrophages, which undergo a shift from an inflammatory phenotype to a reparative one.

The PDGF is a potent inductor of MSCs' mitogenesis and it is the first responsible for collagen synthesis and secretion with consequent connective tissue healing. Moreover, it is a potent inductor of MSCs' chemotaxis.

As the PDGF, the EGF is a potent mitogen and increases the expression of all the genes involved in DNA synthesis. It is fundamental in the metaplastic processes and the epithelial regeneration, and in general, in the reversal of the mucosal atrophy. It can promote the chemotaxis of endothelial cells and stimulate the proliferation of epithelial and mesenchymal cells.

All these properties expressed by the GFs contained in the PRP pointed it out as a promising candidate for submucosal injection aimed toward the regeneration of the mucosal atrophy.

However, still, a lot of open issues remain regarding, most of all, the vast range of PRP kits and preparation methods available on the market. In reality, speaking about PRP constitutes a significant simplification because there is wide variability among the different products available on the market, in terms of absolute platelet number and capacity to concentrate the platelets.

Several classification criteria have been proposed, even though no one has been widely accepted yet.

The so-called DEPA classification proposed by Magalon [8] and colleagues is the most complete that we have available at the moment. It considers four main parameters: the dose of the platelets reported as the absolute number over the volume; the efficiency of the method to concentrate the platelets; the purity of the product in terms of contamination by leukocytes or red blood cells; and the activation of the product with an exogenous clotting factor.

Even though this classification is quite exhaustive and complete, often, many of the parameters are not reported in the different studies. Moreover, the impact of the different parameters on the efficacy of the PRP preparations is not clear yet.

It has not been established yet if a minimum number of platelets or a minimum concentration capacity is required to have an efficacious PRP preparation. Furthermore, the activation is also a debated point. As mentioned above, the activation triggers the platelet degranulation and the sudden release of all the GFs contained inside the granules, while not activating the platelets allows a longer but a slower release of the GFs. It is not validated yet if one modality is better than the other.

The use of PRP in patients with atrophic rhinitis is mainly intended to improve the mucosal trophism, while it has a relative effect on volumetric augmentation of the turbinates. Nonetheless, the PRP has demonstrated, in vitro, to be a potent inductor of osseous differentiation of MSCs. This effect has not been highlighted on the turbinate yet, but it could be a future mechanism to be investigated.

The PRP has been used alone or in combination with the lipoaspirate in the so-called *platelet-rich lipotransfer* (PRL). The combination of PRP with the lipoaspirate allows enhancing the proliferation and the survival of the ADSCs, as mentioned above.

The PRP alone has also demonstrated its benefits on the mucosal atrophy and the subjective symptoms. In our experience, the submucosal injection of PRP was able to improve the SNOT score at 6 months and to reverse the mucosal atrophy.

The use of PRP in the atrophic rhinitis is still under evaluation. Even though it seems to have a benefit, especially in the mucosal trophism, the data supporting a routinely use of PRP are still few and with a low quality of evidence. Furthermore, the regulatory situation for PRP use is not uniform across different countries and this could constitute a limitation to its application. New studies are investigating the use of PRP in atrophic rhinitis and ENS, and they could hopefully provide a more thorough insight into its efficacy.

12.1.3 Placental Extract

The *placental extracts* are a lysate of human placental tissue, which is collected at full-term delivery. They are sterile and acellular compounds. They can be broadly classified into two groups, alcoholic and aqueous placental extracts. The aqueous extracts contain mainly steroid hormones, peptides, and amino acids. Each milliliter of the placental extract is derived from approximately 0.1 g of fresh placenta [9].

Several authors described analgesic, anti-inflammatory, cytoprotective, and radioprotective effects of the placental extract, and according to some authors, it can stimulate cellular proliferation and reparative processes. In vitro, it can increase the proliferation of cord blood cells and fibroblasts.

Furthermore, the placental extract seems to accelerate the wound healing process and to exert immunomodulating effects.

Multiple mechanisms have been proposed to explain the effects of the placental extracts. In vivo evidence in animal models showed that the placental extract could enhance the resistance to the oxidative stress. Their antioxidant properties seem to be correlated to the content in α-fetoprotein.

In vitro, they were able to reduce the oxidative and radiation damage to the cells, increasing the colony formation capacity of progenitor cells, while decreasing the levels of free radicals and inflammatory cytokines, including IL1, IL6, and TNF [10].

The proposed mechanism of action of placental extract in wound healing is mediated by an early rise in the TGF-β levels, followed by an increased VEGF production in the late phase of the healing process, which parallels higher FGF levels and the amplification of the angiogenetic process, a thing that is revealed by an increased expression of CD31.

Nonetheless, many mechanisms behind the effects of the placental extract are far to be understood, as the role of the fibronectin-III and its role in the regulation of the nitric oxide balance.

The placental extract is used as submucosal injection to treat the primary atrophic rhinitis. The earliest report of its efficacy dated back to 1977.

One of the few randomized controlled trials about the treatment for atrophic rhinitis assigned 30 patients with primary atrophic rhinitis to three different treatments: placental extract, oral rifampicin, and a control group treated with alkaline nasal douching [11]. The outcomes were measured at 12 weeks. The subjective symptoms were evaluated alongside with several histological and endoscopic parameters.

The oral rifampicin showed a significant improvement in all the histological parameters considered (conversion toward normal epithelium, inflammatory cells, fibrosis, glandular atrophy, vascularization) when compared to the placental extract and the control group.

The placental extract demonstrated only a reduction of the inflammatory cells versus the control group.

The endoscopic data showed a reduced crusting and nasal secretions, both in rifampicin and placental extract groups compared to the control group. The placental extract was able to reduce the size of the nasal cavities. This effect was explained

by the authors mainly as an effect of increased nasal congestion and it disappeared at the treatment discontinuation.

All three groups showed an improvement in the subjective symptoms at 2 weeks already, which remained stable until the end of the 12 weeks of treatment. Upon therapy discontinuation, the control group was the first to have a relapse of all the subjective symptoms at 2 weeks, while the placental extract group experienced a relapse at about 3 months. The rifampicin arm remained symptoms free for about 1 year of follow-up, with only a relapse of mild crusting for the 30% of patients.

In conclusion, few data are available regarding the use of the placental extract in atrophic rhinitis. According to the literature, it has only a mild effect in primary atrophic rhinitis, while it has not been tested in other forms of atrophic rhinitis yet. The data are too scarce to recommend its use, even though the placental tissues could be an interesting option for the future development of new therapeutic options. In particular, the mesenchymal cells derived from the placental tissue showed a significant immunomodulating capacity through a secretome, which can shift the microenvironment from a pro-inflammatory/pro-fibrotic to a pro-regenerative one.

12.1.4 Resorbable Fillers

One of the main effects of atrophic rhinitis is the abnormally increased volume of the nasal cavities. This lack of airflow resistance causes a relevant dysregulation of the nasal airways' resistance, which grounds many of the subjective symptoms experienced by the patients.

The resorbable fillers have many advantages, including their optimal biocompatibility and their easy use and diffuse availability. Naturally, one of the main drawbacks is their relatively short time to complete resorption (ranging from 6 to 12 months, depending on the product use), which candidates them only as a temporary solution. Nonetheless, their use could give a useful hint in understanding if the patient would benefit in terms of symptoms from an augmentation of the turbinates' volume and a reduction of the space in the nasal cavities. They could be a temporary solution in the prevision of a more definitive one.

The products tested for submucosal injection into the turbinates were the *hyaluronic acid (HA)* and carboxymethylcellulose/glycerin gel.

The HA is a standard component of the extracellular matrix in the connective tissue and has been used for many years as a resorbable dermal filler for many purposes, mainly in aesthetic medicine.

The HA is a linear polyanionic bio-polysaccharide, which is part of the category of the glycosaminoglycans. It exists in different molecular weights, which influences its biological and chemical–physical properties and consequently, its suitability for specific indications [12]. It is incredibly versatile and has a unique viscoelastic nature that characterizes it as a reversible gel. The HA, as it is, is easily enzymatically degraded in half a day. However, the so-called cross-linking process introduces points of resistance to enzymatic degradation and increases its permanence in the injection site and the gel viscoelasticity, i.e., the rigidity of the polymer network.

The HA is highly negatively charged, a thing that allows a high degree of hydration when injected into the tissues. Furthermore, it undergoes a process of isovolemic degradation, which means that, when a molecule is resorbed, the other remaining molecules can absorb higher quantities of water. This property allows maintaining a constant volume even during the degradation process until the last HA molecule disappears.

Moreover, it is available on the market an enzyme called hyaluronidase, which can break up the HA molecules, thus causing their rapid resorption in case of wrongly made injection.

The use of HA submucosal injections in patients with ENS was tested in a small group of patients [13]. A CO_2 laser was used to make small holes in the mucosa, in the front part of the head of the turbinate, where a 25G cannula was inserted. Under direct vision, 0.3–0.4 ml of HA was injected, in a retrograde fashion. HA was also injected with the same modality under the perichondrium of the nasal septum. The procedure was performed bilaterally. The use of a blunt cannula intended to avoid excessive damage to the mucosa and at 1-week control, no reaction to the HA or extrusion of the material was noted.

According to the authors, the patients experienced clinical improvement with the sensation of increased nasal airflow, reduced crusting, and perception of dry secretions. Rhinoscopy and acoustic rhinometry at 7 days, and 3 and 6 months after the injections demonstrated substantial stability in the volume of the HA and confirmed a reduced nasal cavity. The symptoms' relief persisted at 3 and 6 months, while it completely disappeared at 12 months as the HA was resorbed completely. However, the symptoms were only generically reported and no validated questionnaire was administered.

The significant water absorption of HA has also contributed to a better mucosal moisturization, at least in part. Nonetheless, the high hydration of HA should be taken into account when injecting because the resulting volume is increased by the water recruited. It is advisable to inject less at the beginning and eventually complete the injection at 7 days if it is necessary.

The *carboxymethylcellulose/glycerin gel* is a resorbable material that was used in otorhinolaryngology as a resorbable filler for vocal fold augmentation, in vocal fold atrophy, paresis, or paralysis. It has a medium duration before resorption between 3 and 6 months, less than HA. It is FDA approved and has a good profile of safety [14].

The patients who could benefit from a temporary augmentation of the turbinates with carboxymethylcellulose/glycerin gel were patients with ENS selected according to a positive cotton test. The cotton test was performed by placing dry cotton pledgets in different parts of the nasal cavities, where a deficiency in the turbinate structure was suspected. A relief in subjective symptoms and increased ease at breathing were considered as a positive cotton test.

The carboxymethylcellulose/glycerin gel was injected in 14 patients, using a 22G needle, in the inferolateral nasal wall, to create bulk and reduce the volume of the nasal cavities. Even though the cotton test guided slight variations, the areas involved by the injections often included the remnant anterior head of the inferior turbinate, the anterior nasal vestibule, and the inferior meatus/lateral nasal wall.

The injections were well tolerated, and no significant adverse reactions were reported. Different validated tests were used to evaluate the benefits of carboxymethylcellulose/glycerin gel injections, in particular the Empty Nose Syndrome 6-Item Questionnaire (ENS6Q) and the 22-item Sino-Nasal Outcome Test (SNOT-22) at 1 week, 1 month, and 3 months.

The benefits in terms of symptoms improvement were noted at 1 week and 1 month. However, at 3 months, the tests' scores overlapped to those at the baseline.

In general, the data available regarding the resorbable fillers are limited and deriving from single-center, small-sized experiences. Resorbable products, given their temporary nature, could be useful in an interlude phase before the invasive surgery, to reduce the symptoms. Furthermore, they could be used to identify more precisely the patients who could benefit most from the surgical procedure and the points in the nasal cavities, where the added volume could elicit the most considerable improvement of the symptoms. However, these potentialities should be further investigated on a broader scale and with a higher quality of the evidence.

12.2 Conclusions

As described in this chapter, submucosal injections could be a promising therapeutic option in the treatment of both the primary and secondary forms of atrophic rhinitis. They have the great advantage of limited invasiveness when compared to surgery, and they could be easily repeated several times over the natural history of the disease. Furthermore, the range of possible candidates is vast, since the choice of different injection materials offers the possibility to cover a broad spectrum of clinical necessities, from the proper volume augmentation to the mucosal regeneration.

The new options given by the regenerative medicine, offer the possibility to have fillers which have a biologically active role in the healing process.

Nonetheless, all the data available about injective submucosal therapies derived from small size samples, non-randomized studies, and provided a generally low quality of evidence. More solid data are needed to recommend these therapies as a standard of care, even though the early results are promising.

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Nasal Septal Perforations: Modern Diagnostic Work-Up, Management and Surgical Strategy

13

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13.1 Introduction

The closure of septal perforations is a challenging procedure in nasal reconstructive surgery, both for the surgeon and the patient, since postoperative care is just as important as the surgical procedure used to obtain the best outcome. The first objective is to restore the nasal function and, in the meantime, to rebuild, as possible, the anatomical integrity of the nasal structures, to have long-lasting results.

The surgical success rate depends on a precise definition of aetiology, state of nasal mucosa, size and location of the defect, and on a correct postoperative management.

13.2 Aetiology and Clinical Features

The aetiology of nasal septal perforations can be classified into the following main categories: traumatic, iatrogenic, inflammatory/malignant, infectious, and drug-related. The prevalence and incidence of this conditions are increasing, also thanks to the rise of new and more specific diagnostic tools described in literature.

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Fig. 13.1 A seventeenth-century human nasal septum showing an oval perforation produced by syphilitic infection

In the Hunterian Museum of The Royal College of Surgeons in London (n.1228), a septal specimen is conserved an important septal perforation of about 1.5 cm can be appreciated; it belonged to a patient suffering for syphilitic infection, who died in the seventeenth century (Fig. 13.1).

According to recent literature [1], nasal septal perforations may be classified based on their size, as follows:

- Small perforations—Diameter ≤0.5 cm
- Medium perforations—Diameter between 0.5 and 2 cm
- Large perforations—Diameter >2 cm

Many nasoseptal perforations remain undiagnosed, especially smaller ones and these patients keep complaining symptoms like crusts, recurrent epistaxis, nasal whistling, or a feeling of impaired nasal breathing due to turbulent air flow.

In 1997, Guyette and Smith [2] stated that posterior rhinomanometry is important to investigate nasal resistance in septal perforations.

Later, Cannon and Others (2013) [3] used computational fluid dynamics technology to report that larger anterior and smaller posterior perforations exhibited greater alterations in wall shear stress and velocity at the site of the perforation. In the meantime, there was relatively little alteration of airflow or conditioning parameters in superior septal perforations.

More recently, Emrah Sapmaz and Battal Tahsin Somuk [4] updated septal perforations classification taking into account no longer their absolute size, but the

ratio between the vertical length of septal perforation and the total vertical length of the septum: the four groups of perforations were so defined:

- Group 1 (small perforation) was defined as length of perforation less than 1/4 of total vertical septal length.
- Group 2 (medium perforation) was defined as length of perforation larger than 1/4 of total vertical septal length and less than 1/2 of total vertical septal length.
- Group 3 (large perforation) was defined as length of perforation larger than 1/2 of total vertical septal length and less than 3/4 of total vertical septal length.
- Group 4 (very large perforation) was defined as length of perforation larger than 3/4 of total vertical septal length.

These authors considered that this ratio of these two measurements could help determine a more realistic perforation size for each patient. While it could be very easy to repair a 2 -cm-long perforation in a patient with a 3.5 -cm-long septal vertical diameter, it could be rather difficult to repair a 2 -cm-long perforation in a patient with a 2.5 -cm septal vertical diameter.

The patient's anatomy is crucial to assess the grade of complexity of surgery. To repair a septal perforation in a patient with a small and short nose is in fact more difficult than to repair the same defect in a wider and larger nose, where a big hump makes the septum larger and higher. In this case, a contemporary reductive rhinoseptoplasty can be performed in order to use the nasal tissue removed from the hump to repair the septal defect and to reassemble nasal elements in a new anatomical configuration.

Despite the accuracy of the diagnostic work-up employed, with both radiological and endoscopic evaluation, according to Romo, the surgical techniques have a high failure rate which could be attributed to two unfavourable factors: an inadequate blood supply and a scarred host bed. Failure rates range from 60% for procedures in the past to 18% for the best of the modern two-stage procedures. Nowadays, more than 90% of small perforations can be closed reliably, and 70–80% of large defects can be completely closed with the latest techniques.

To investigate the blood supply, angiography-computed tomography can be performed during the preoperative diagnostic work-up, in order to obtain a 3-D sight of the septum and its vascularization near to the perforation. This way surgery can be planned to reach the best outcome (Fig. 13.2).

13.3 Diagnostic Modern Work-Up: Imaging and Elaborations

Anterior rhinoscopy is essential in the first examination of the patient as it may demonstrate the configuration of the perforation, the presence of crusting, and the irregularities of the mucosa, but nasal endoscopy remains mandatory to investigate all the nasal fossa of both sides and the relationship with turbinates and the inferior meatus.

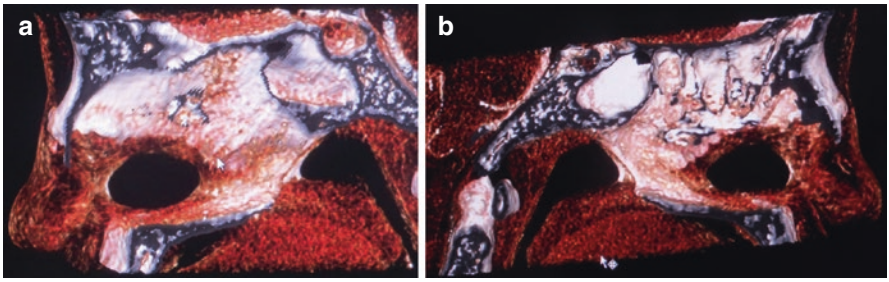

Fig. 13.2 (**a**, **b**) Three-dimensional angio-CT reconstruction left and right side of a female patient, 39 years old, with a 20 mm iatrogenic perforation

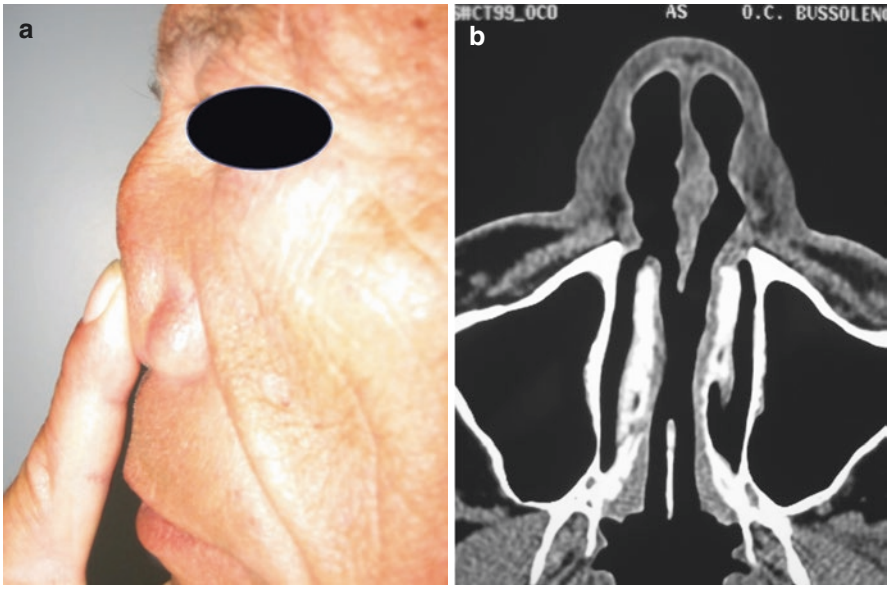

Fig. 13.3 (**a**) The tip of the nose collapses under the pressure of a finger. (**b**) CT scan shows a large perforation of the nasal septum

Physical examination of the nose begins with an evaluation of the external nose. Large perforations may result in loss of support to the dorsum of the nose and subsequent saddle nose deformity and sometimes a collapse of the anterior part of the pyramid like in the patient shown in Fig. 13.3a. The patient with his finger could press the anterior nose.

Often the size of the perforation of the cartilage or of the bone is wider than what it is visible on the mucosa during anterior rhinoscopy, and therefore, it should be better assessed with radiologic imaging (Mocella 2013) [5] (Figs. 13.4 and 13.5).

In the diagnostic work-up of septal perforation, a lot of detailed laboratory investigations can be performed. In the suspect of cocaine abuse, for example, it is

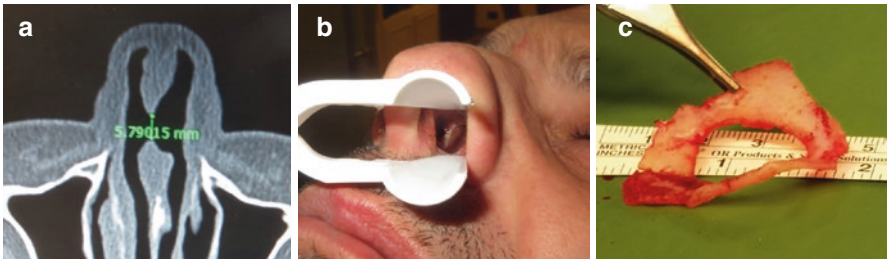

Fig. 13.4 (**a**) CT scan of a 5.79 mm septal perforation, (**b**) Anterior rhinoscopy shows the small mucosal perforation. (**c**) In the extracorporeal reconstruction the cartilage defect is bigger than 2 cm

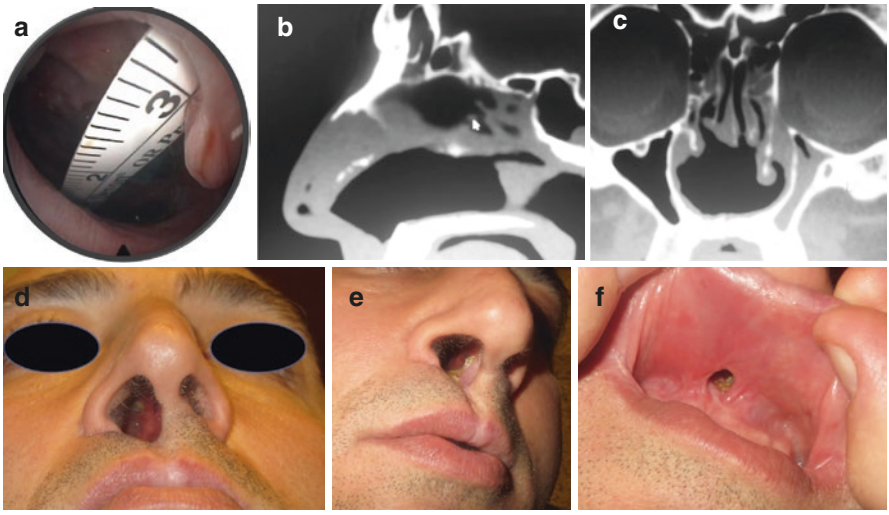

Fig. 13.5 (**a**) Endoscopic view of large septal perforation (4 cm) in cocaine user. (**b**, **c**) CT scans show near-total septal absence. (**d**, **e**) The defect involves the soft tissues of nasal philtrum. The scar indicates a previous unsuccessful surgery. (**f**) Oronasal fistula which ends in the upper oral vestibule

recommended to run blood and urine tests to detect cocaine catabolites, to find out its recent use, which patients usually do not easily confess. It is also possible to test the hair to make sure the patient has not been using cocaine during the 6 months before the operation. In these patients, in fact, surgery can be planned only if they have reliably quit cocaine snorting for at least 1 year.

Before considering surgery, it is important to cure the nasal mucosa in order to obtain a good surgical field for suturing, which increases the changes to rebuild the nasal structures successfully.

Vasoconstrictor medicaments should be stopped at least 2 months before the surgical approach to avoid bleeding during surgery.

We also suggest to cure nasal fossa with special ointments, containing mentholum, aetherol eucalypt, vitamin A, vaselinum, and hyaluronic acid for 1 month before the procedure. The preoperative care includes lavages with frequent saline nasal irrigations or water picks.

Topic medications used as emollients and antibiotic treatment to avoid infection are mandatory before surgery.

According to Romo 2018 [1] ,"the surgeon must stabilize the nasal mucosa and decrease inflammation before repair is contemplated. Success of the repair depends on the condition of surrounding tissues, cartilage, and blood supply."

To achieve the best assessment of nasal structures and framework in case of septal perforations, a specific preoperative radiologic work-up, with elaboration techniques of imaging, is able to detect and quantify the bony loss under the mucosal layers, in order to obtain the exact measure of the defect and to plan its surgical repair. The same technique can be used during post-surgical follow-up to evaluate the outcomes (Mocella et Others 2013) [5] (Fig. 13.6).

Multidetector CT scanners with 16 detector rows (or more) allow the acquisition of volumetric data sets that can be electronically reconstructed in any plane.

This technique gives radiologists and surgeons the opportunity to visualize the anatomic structures in paranasal sinus diseases and nasal septum repair, and all the residual tissues that are present in greater detail may help increase the accuracy of diagnosis and therapeutic planning.

The images were reconstructed at a standard vendor workstation (Wizard; Siemens) and at a standard PACS Workstation (Synapse, Fujifilm Medical Systems, equipped with Voxar 3D 6.3 software).

Each reconstruction is tailored to better depict the structure of clinical interest: the nasal septum, lateral nasal wall, and paranasal sinuses.

The anatomic location and orientation of the structures to be evaluated are confirmed on images in three orthogonal (axial, coronal, and sagittal) planes of reference.

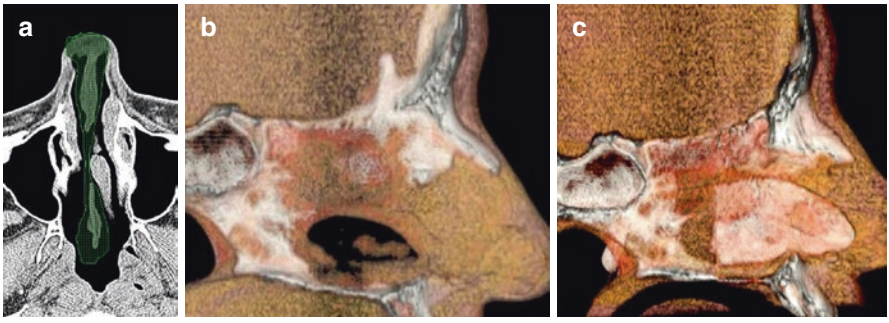

Fig. 13.6 (**a**) CT scan shows a septal perforation. (**b**) 3-D VRT reconstruction of a sagittal CT scan where a large inferior septal perforation is visible. (**c**) Post-surgical 3-D VRT reconstruction of a sagittal CT scan, the heterologous fascia positioned between the mucoperichondrial flaps used to repair the defect is visible

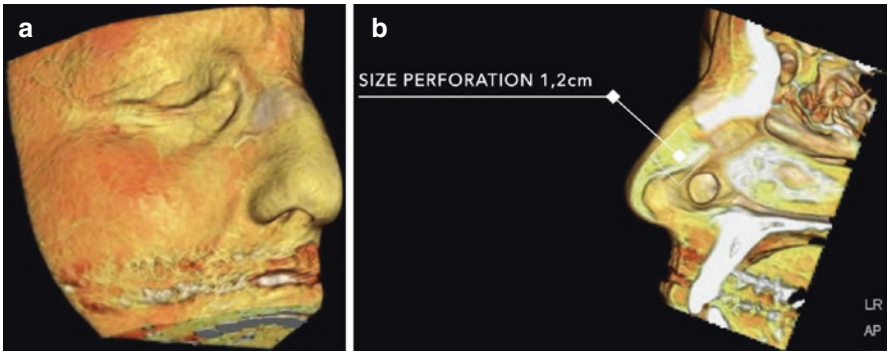

Fig. 13.7 (**a**) 3-D VRT reconstruction of the patient's face. (**b**) 3-D VRT reconstruction of a sagittal section of the patient's head shows a septal perforation (1.2 cm)

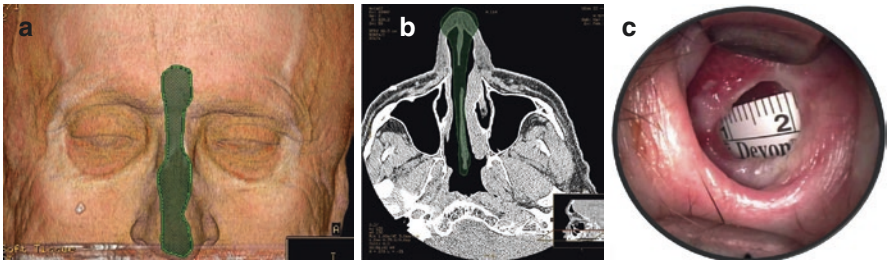

Fig. 13.8 (**a**) The area of the nasal septum and nasal tip are circled on the axial 3-D VRT reconstruction of the patient's face. (**b**) The same area is circled on the CT scan, the anterior septal perforation is visible. (**c**) The septal perforation is visible at the anterior rhinoscopy and measured

3-D VRT (volume rendering technique) and animated three-dimensional reformatting images were obtained to achieve the best overview of morphology and local anatomy, integrating the 2D information, thus providing an excellent preoperative "road map" and planning tools (Figs. 13.7 and 13.8).

13.4 Management and Surgical Techniques

When planning treatment, it is possible to choose between two different options:

- Nasal septal prosthesis placement
- Surgical repair procedure in one or more steps

The **prosthesis** can be made out of acrylic, plastic, or silicone.

Nowadays, it is better to use the silicone material, and the prosthesis is available in multiple round and oval shapes, sizes, and thicknesses.

Fig. 13.9 (**a**) Silastic prosthesis with oval configuration; (**b**) introduction of a template to verify exact position of the device; (**c**) introduction of silastic in the nostril

The placement requires that the remnant septum, anterior and posterior to the perforation, is straight and the margins of perforation must not show hypertrophic mucosa. If these conditions are not respected, a simple septoplasty to straighten the remnant septum, or topical therapy of radiofrequency, may cure the mucosa before the main reconstructive procedure is performed (Fig. 13.9).

Recently, to obtain a more accurate size of the prosthesis, a 3-D printing method for nasal septal perforations resulted in a higher retention rate and more tailored graft, which lead to an improvement in the sensation of air flow (Onerci and Others 2016) [6].

Despite the various surgical techniques described this far, there is not a standardization of the procedures and several techniques can be classified broadly into several groups, from the most conservative to the most radical ones (Romo 2018) [1].

In this chapter, the authors prefer to divide techniques according to the level of difficulty and the involvement of surrounding structures as follows:

1. Endonasal approach with the employment of nasal structures and local flaps
2. External open approach through the columella and reconstructive rhinoseptoplasty
3. Reassembled endonasal bone and cartilaginous structures with or without biomaterial
4. External approach with major access to the nasal structures like alotomy, or midfacial approach or facial flaps
5. External approach with a pericranial flap with a bicoronal approach
6. Radial forearm flap

The first to describe some surgical techniques in the modern era to repair septal perforations was probably Cottle in 1958 [7].

In his book, *Secondary Rhinoplasty*, Rudy Meyer [8] described his original technique dated in the 1968 and his method was then modified by Hinderer in 1973 [9] and Tardy in 1977 [10]; it was a three-stage procedure with a gingivobuccal flap reinforced with an ear cartilage graft sutured to it. This method was utilized especially for large perforations in cocaine users.

In 1977, Tardy proposed a sublabial mucosal flap [10].

In 1980, Fairbanks [11] described bipedicled mucosal advancement flaps with an underlying connective tissue autograft. In 1986, Bridger [12] described a two-procedure plan with a nasolabial flap to repair defects larger than 2 cm. Defects larger than 4 cm were considered inoperable as the local mucosa was not sufficient.

Mobley et al. 2001 [13] treated a 38-year-old man who had a large septal perforation caused by chronic inhalation of cocaine. They were able to repair the perforation with a left radial forearm free flap. Long-term follow-up indicated a successful closure of the defect and a natural thinning of the flap.

For more extensive perforations, the use of facial artery musculomucosal (FAMM) pedicled flaps has been described by Ayad and Others (2015) [14]. The flap is raised along the intraoral course of the facial artery (demarcated with Doppler imaging) to the gingivobuccal sulcus region.

It is a versatile locoregional pedicled flap that tunnelled into the nasal cavity provides tissue vascularization for larger perforations, even if it is considered a challenging technique.

All these techniques include local flaps, various autologous, homologous, and biocompatible grafts, two or more stage procedures, and free-flap repair. The use of endoscopy could very often provide a better visualization during such procedures, giving the opportunity to chose the right position where to put more stable sutures in order to improve the final result.

Many authors have used endoscopic treatment, like Giacomini [15], Cassano [16], Presutti [17], Castelnuovo [18], Re [19], and Tasca [20], with good results, but when compared with the rest of the world, there is no agreement on the use of multiple layers during surgery. In his analysis of 15 different authors, Cassano found out that only three of them were able to close perforations with the method of one or maximum two layers: Hanci [21], Castelnuovo [18] and Lee [22]. All the others used three layers. Anyway, the relative percentage of success was high, depending mostly on the selection of the cases presented.

According to Romo (1988) [23], he reported surgical approaches that include external rhinoplasty, midfacial degloving, unilateral hemitransfixion, and closed endonasal techniques. The advantage of the latter is that it does not leave any external scar, but it is more difficult to perform due to the narrow operating field.

"Open" techniques offer a wider operating field, thus allowing better access to the superior and posterior margins of the perforation.

According to Rudy Meyer (1988–2002) [8], a great master of surgical septal repair and reconstructive secondary noses, the extramucosal techniques are extraordinary helpful, so that he abandoned the use of local flaps and adapted the designed technique to fit the individual situation.

In 1986, Kridel [24] suggested the septal perforation closure using the external rhinoplasty approach, and in 1995 [25], the major goal in septal perforation surgery was not only to repair the perforation but also to restore normal form and function to the nose. The increased surgical exposure provided by the open approach in fact not only facilitated the repair of large and posterior perforations but also allowed performing contemporary secondary rhinoplasty. In 1998, the same author proposed the repair of septal perforation with acellular human dermal graft with high rate of success.

In a work of 2006, Foda [26] presented his experience with an open approach and a bipedicled superior and inferior flaps with interposed graft in the site of perforations from 1 to 5 cm with a success rate from 70 to 90% and a cosmetic satisfaction of 95%.

In 2007, Ribeiro [27], from Brazil, presented a high successful series of cases, 258 in patients with a perforation of 1–3.5 cm, who were treated with the employment of a bipedicled technique in open approach and an interposed graft in closed approach with a cosmetic result and patient satisfaction of 98.8%.

In the same year, Fernando Pedroza [28] in his review of 25 years of experience presented his results in the septal perforation repair using his technique that consists of subperichondrial/periosteal dissection, rotation of nasal mucosa for tension-free closure, with no mucosa incision if possible, and a multilayer closure with interposition graft. He used this internal approach to repair defects between 1 and 3 cm, with a 97% rate of success.

Kridel (1995) [25] in a previous paper affirmed that the possibility to correct septal perforations and nasal external deformities in a unique set presents great technical difficulties and only some selected cases, in which perforation is small and a dorsal hump can be removed, are appropriate for synchronous correction.

More recently, though, Kridel and Delaney (2017, 2018, 2019, 2020) [29–32] published their vast experience on 141–180 patients in 31 years of observations and concluded that "in experienced hands, septal perforation repair may be performed simultaneously with primary or revision septorhinoplasty via an open approach and furthermore, as most intranasal mucosal advancement flap methods recruit mucosa from above or below the perforation, a perforation's vertical dimension is more important than its horizontal front-to-back length."

His technique consisted in positioning a connective tissue graft placed between the repaired septal graft (AlloDerm, LifeCell Corp.®), but in Europe, this material is not authorized; therefore, general tissue grafts 4 × 5 cm, or more if necessary, of Tutopatch® porcine pericardium are used.

Septal perforations generally have an oval shape, with a cranio-caudal diameter shorter than the antero-posterior one. This feature is particularly useful when it comes to close the hole. After the dissection of the osteo-cartilaginous vault and the muco-pericondrium from the undersurface of the upper lateral cartilage of the bony vault, in fact, it is easier to pull down the upper portion of the section to reach the inferior border of perforation, with a contemporary reductive rhinoplasty.

Large perforations, with a cranio-caudal diameter shorter than the antero-posterior one, can also be managed with an external approach, especially when a reductive rhinoplasty is also needed to eliminate a dorsal hump. The cartilage obtained from the hump, in fact, can be combined with the fragments obtained from the remnant septum to model a graft, covered in biocompatible fascia, that can later be used to close the large septal perforation (Figs. 13.10 and 13.11).

Sometimes, a more consistent material, like Fortiva® of 1.5 mm (porcine dermis), can be positioned more posteriorly, to close defects of the posterior septum, in order to raise the chances of success.

Endonasal approaches can also be employed when combining reductive rhinoseptoplasty with septal repair. Even in this case, the cartilage obtained from the hump can be covered with fascia, at least on one side, and then repositioned between the two sutured layers of septal mucosa, to close the perforation (Fig. 13.12).

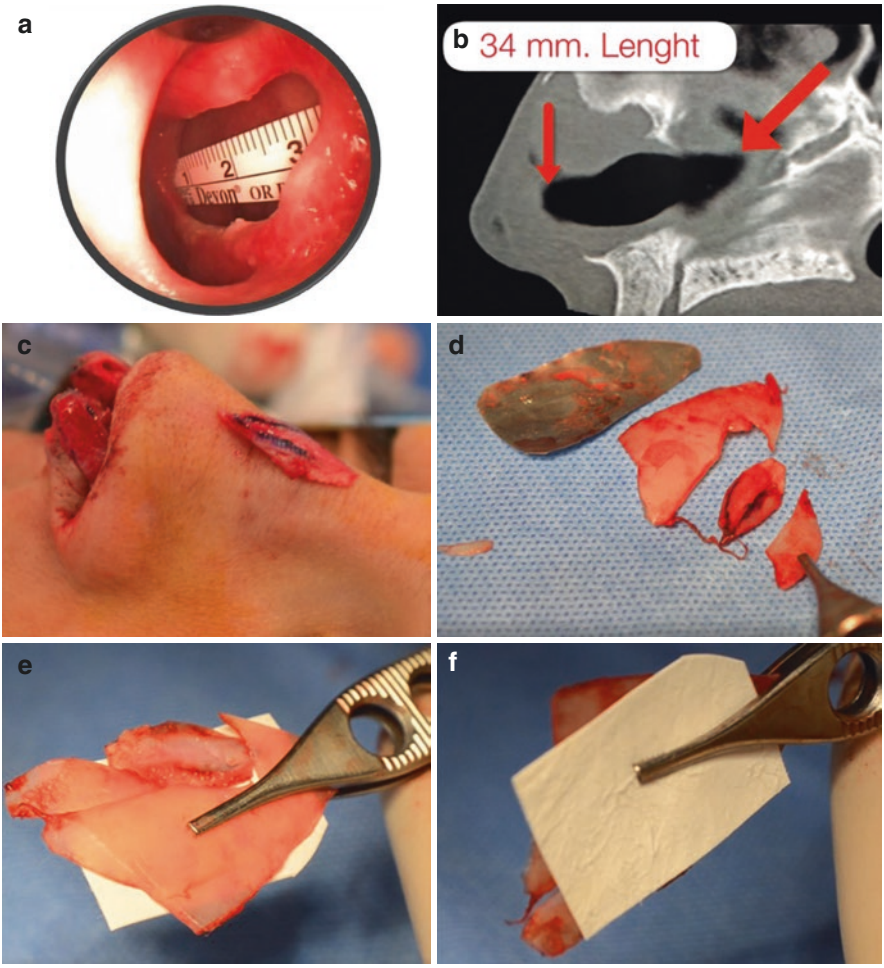

Fig. 13.10 (**a**) Endoscopic view of a large perforation. (**b**) Sagittal CT scan shows a perforation of 34 mm length. (**c**) Hump removal during a reductive rhinoseptoplasty with an external approach for septal perforation. (**d**) Septal residual graft, comprehending the hump, in extracorporeal reconstruction and template. (**e**, **f**) Reassembled septum with fascia on left side

Reviewing our personal series of 105 patients, who underwent a surgical procedure for septal perforation in the last 15 years, a reductive rhinoseptoplasty was performed with the principal aim to obtain more tissue in the same operatory field and to have the possibility of increasing the transfer and movement of flaps to cover the defect.

More recently, especially for perforations with a major diameter larger than 3 cm and normal size of the nose, without a great amount of original septum, bank rib cartilage has been used with the aim to reinforce the defected septum.

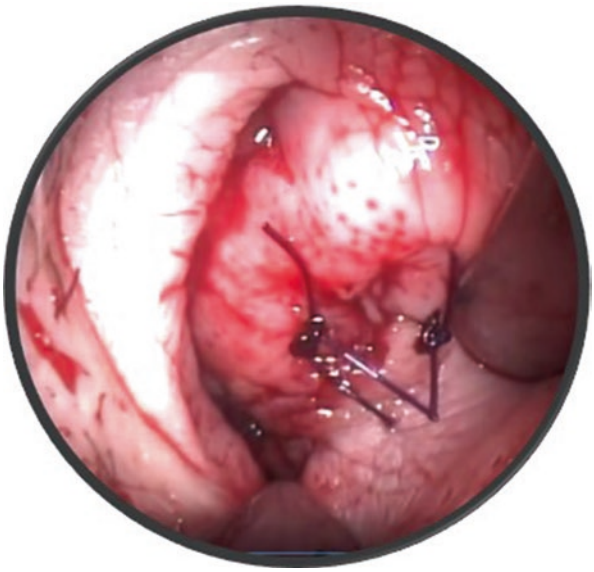

Fig. 13.11 Suture of the right side of septal mucosa with long-term sutures

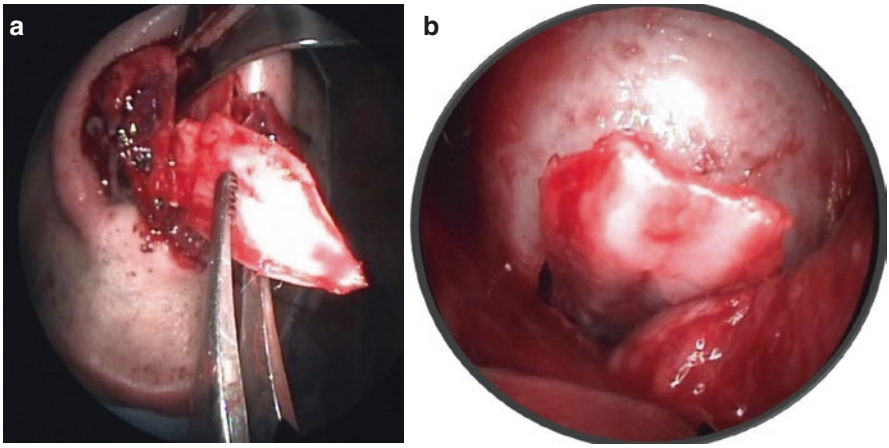

Fig. 13.12 (**a**) Hump introduced between the two sutured mucosal layers; (**b**) The graft is positioned just in the place of the septal defect

During extracorporeal reconstruction, fragments of the dissected septum can be remodelled to build a new septum, with the rib cartilage positioned on its posterior edge. It can be hence covered in fascia and reimplanted in the nose (Fig. 13.13a–r).

In both open and closed or endoscopic approaches, the interposition inside the sutured mucosa of graft material of different origin leads to better and long-lasting results, both functional and aesthetic.

According to Kim and Rhee 2012 [33], "the size of perforation was the most significant factor for complete closure. Surgical failure occurred more frequently in

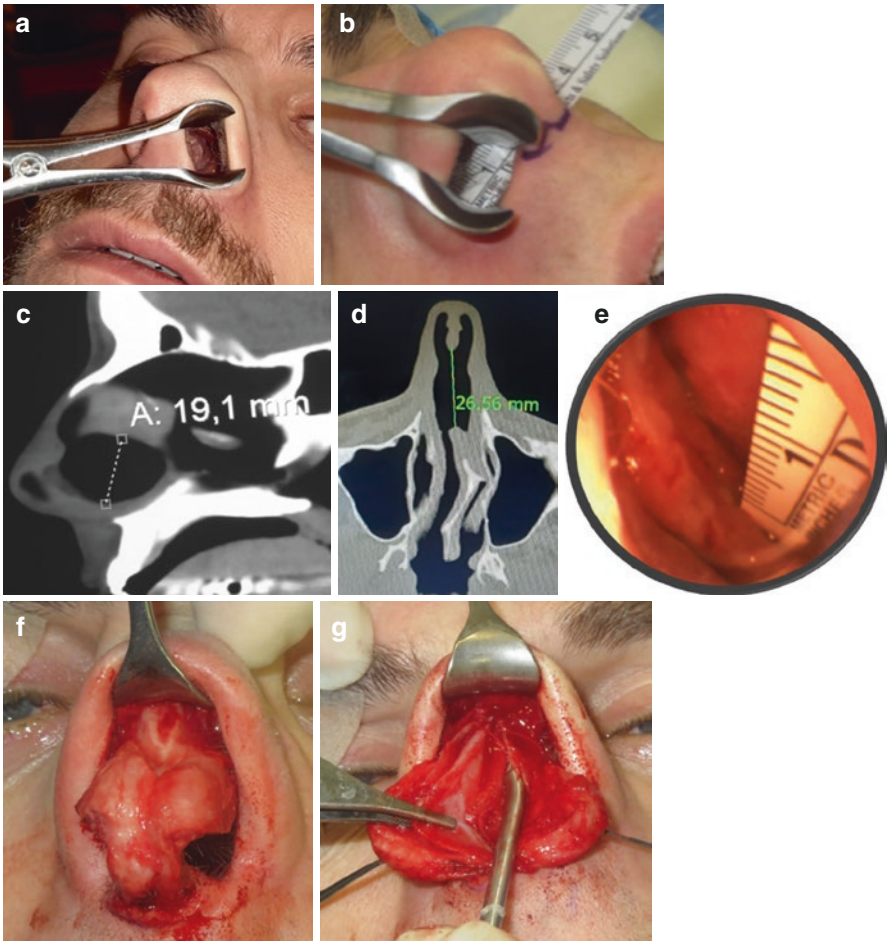

Fig. 13.13 Clinical case: male patient age 37 years old, previous use of cocaine 20 years before. (**a**) Anterior rhinoscopy. (**b**) Anterior rhinoscopy from the right nostril, with a centimetre in the left nasal fossa. (**c**) Sagittal CT scan with the evidence of the perforation, with a the caudo-cranial measure of 19.1 mm. (**d**) Axial CT scan with a measure of antero-posterior defect of 26.56 mm and a deviation posterior to the septal perforation. (**e**) Endoscopic view of the perforation, which is wider than 2 cm. (**f**) Alar cartilages exposed during open approach. (**g**) Dissection over the site of perforation. (**h**) Complete dissection just near the perforation with extramucosal method. (**i**) Penetration of the knife inside the perforation. (**j**) Completed dissection all around the perforation. (**k**) The residual septum is extracted and measured to plan the reconstruction. The perforation is bigger than it seemed on the endoscopic evaluation, but its dimension almost matches the measurement made with the CT scan. (**l**) The residual septum in some modelled pieces and the rib bank cartilage that will be sectioned and fashioned as necessary. (**m**) Septal reconstruction graft with the rib cartilage positioned on its back. (**n**) The piece is covered with bovine pericardium tailored as necessary before introduction in the mucosal layer sutured. (**o**) Postoperative sagittal CT scan shows the success obtained with the reconstructive rhinoseptoplasty. (**p**) Anterior rhinoscopy in the right nasal fossa shows the septum repaired. (**q**) Preoperative lateral profile. (**r**) Postoperative profile with a new nose

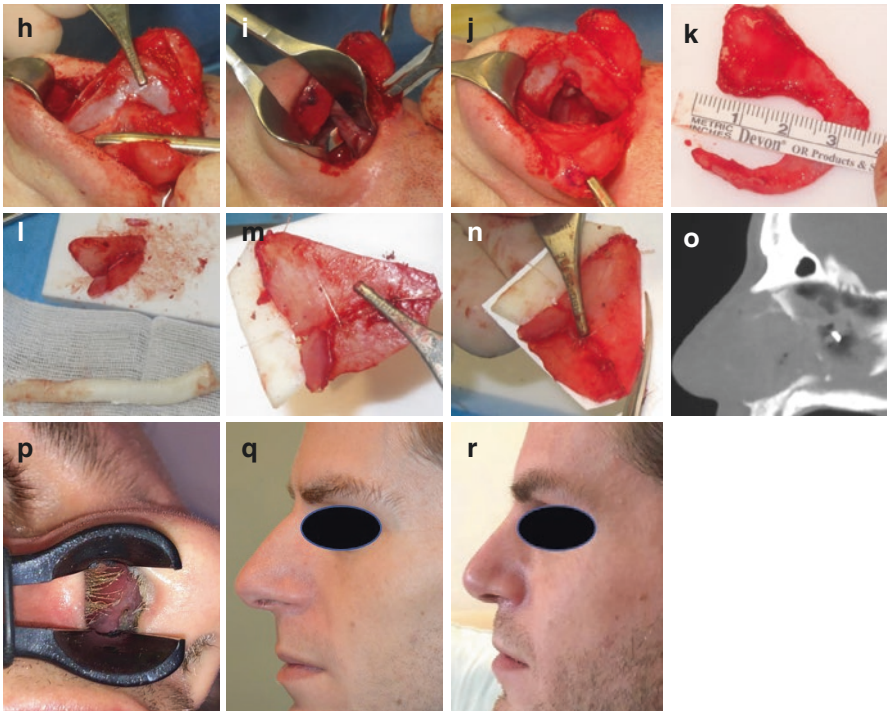

Fig. 13.13 (continued)

patients with large perforation (>2 cm) than in those with small-to-moderate perforation (≤2 cm). The bilateral coverage over the perforation with vascularized mucosal flap also helped complete closure. Interposition of grafts appeared to assist complete closure, although it was statistically insignificant." This concept, tough, could not apply to larger perforations, when it is not always possible to close both sides and a retraction of tissue is possible.

Flavill E and Gilmore JE (2014) [34] reported a technique for septal perforation repair that did not rely on intraoperative mucosal closure of the perforation defect. Their patients received multilayer interposition grafts and no attempt at intraoperative mucosal closure to repair septal perforations. They utilized multilayer interposition grafts consisting of temporoparietal fascia on one side, polydioxanone plate in the middle, and deep temporal fascia on the other side, or acellular dermal matrix, polydioxanone plate, and full-thickness temporal fascia. In these cases, Silastic or silicone sheets were placed bilaterally for at least 12 weeks to protect the septum during healing.

This technique was applied to a variety of challenging surgical candidates (Fig. 13.14).

Ferreli and Castelnuovo (2017) [35] in a chapter of the book of Alobid and Castelnuovo (2017) [35] proposed an algorithm for endoscopic-assisted repair of septal perforations in which they affirmed that the interposition of a graft between

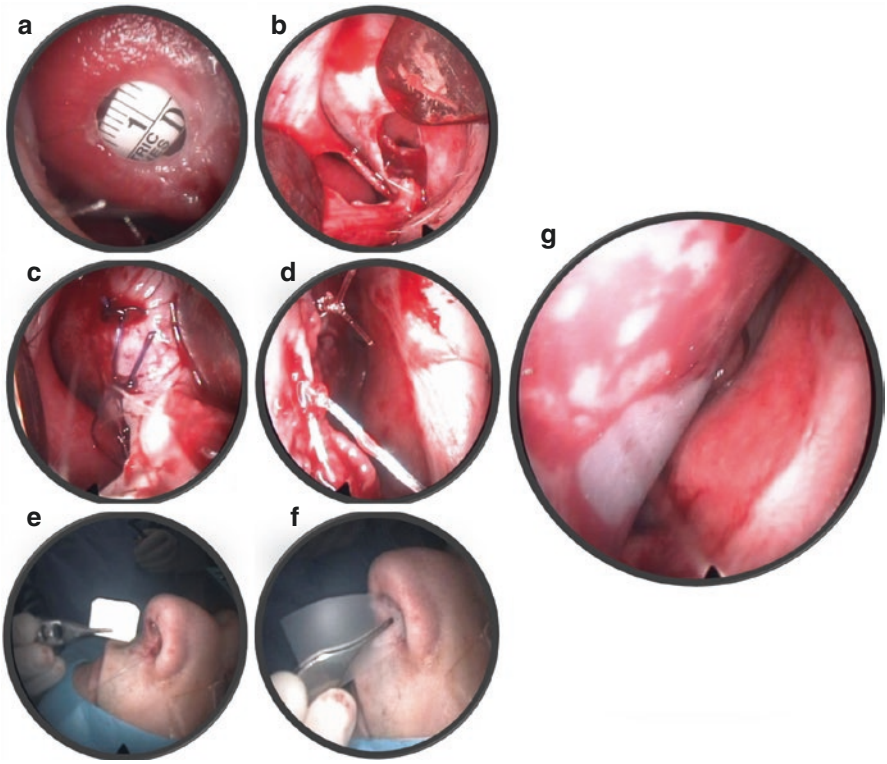

Fig. 13.14 (**a**) Septal circular perforation of 1 cm diameter. (**b**) Dissection with the nasal speculum into the virtual space between mucosa and cartilage; it shows the perforation on both sides. (**c**) Suture of the right side. (**d**) Suture of the left side. (**e**) Introduction of fascia and crushed cartilage inside the nose. (**f**) Positioning of silastic sheet in the nasal fossa. (**g**) Septal appearance under the silastic sheet positioned in the left side of nasal fossa

the two mucosal layers is useless for small- to medium-sized perforations, while they suggest the use of lateral nasal wall flaps, facial artery musculomucosal flap or pericranial flap, and conchal cartilage in large defects, where a complete reassembling of nasal structure and probably an extensive open approach and more cartilage are often necessary.

13.5 Conclusions and Perspective

Septal perforation repair is a challenging procedure both for the patient and for the surgeon.

Many procedures have been described in literature, especially in the recent years, but no uniformity of treatment can be recognized. Different approaches can be used, with a variable percentage of success.

Surgeons dedicated to this purpose are not so widespread in each country and not always can assure the postoperative results, due to the difficult management and variable conditions. In order to raise the possibilities of success, patients must be correctly studied before surgery and they often must undergo preoperative preparation. Postoperative follow-up and care, on the other hand, are also greatly important to assure the surgical outcome.

The nasal mucosa, in fact, needs some months to heal after the operation, given its previous atrophic state, caused by the impaired intranasal ventilation. Once the mucosa has recovered and the perforation has been surgically closed, patients usually report an improved sensation of nasal airflow.

This complex surgery is well tolerated by the patient, but he has to be advised of the probable necessity of further surgical procedures to complete the work, especially for large perforations.

Nowadays, new materials can be used to repair septal defects, mesenchymal stem cells, for example, are more and more present in modern studies worldwide; as well as cartilage regeneration can be employed without harvesting tissues with more aggressive methods [36].

In any case, surgery must be aimed to obtain the best aesthetic and functional results so to improve the quality of life of the patients, with the smallest discomfort possible for them.

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Surgical Treatment of Atrophic Rhinitis: The Use of Autografts in Nasal Dorsum Repair

14

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Abbreviations

ANS	Anterior nasal spine
DC	Diced cartilage
DCF	Diced cartilage fascia
ENS	Empty nose syndrome
LLC	Lower lateral cartilage
PAR	Primary atrophic rhinitis
SAR	Secondary atrophic rhinitis
SEG	Septal extension graft
SSTE	Skin and soft tissue envelope
ULC	Upper lateral cartilage

14.1 Introduction

Atrophic rhinitis is a distressing nasal condition characterized by atrophy of the nasal mucosa, abnormal patency of the nostrils, crust deposition, and foul smelling.

Histology specimens show atrophy of the serous and mucous glands, loss of the cilia and goblet cells, and chronic infiltration of the lamina propria with granulations and scars. These histological changes are responsible for altered mucociliary

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transport, which leads to the stagnation of secretions and promotes the formation of crusts that may ultimately be a source of recurrent bacterial infections [1].

Long-standing atrophic rhinitis in addition may produce a deformity known as "saddle nose", due to absorption of the nasal bone and/or the septal cartilage.

Nasal bridge depression may in fact be seen in many cases of chronic atrophic rhinitis [2].

A possible explanation of this event is the increased concentration of alkaline phosphates in atrophied nasal mucosa that can be responsible for the absorption of bone and cartilage [3].

In primary atrophic rhinitis (PAR), which is characterized by metaplastic processes of the nasal mucosa (epithelium, glands, and vessels) and by the activation of the osteoclasts responsible for bone resorption, the cases of saddle nose are more serious since both cartilaginous and bone structures are involved.

Secondary atrophic rhinitis (SAR) develops from an underlying disease or may result from previous therapeutic measures. In contrast to PAR there is no osteoclastic activity, so the term "diffuse atrophic rhinitis" may be more appropriate.

Pathogenetic factors leading to SAR include: endonasal surgery, for example: partial removal of the lower and/or middle nasal turbinates (56%) or maxillectomy (6%) and nasal trauma requiring surgical reconstruction (1%).

A particular kind of post-surgical condition is called empty nose syndrome (ENS) [4]. It is defined as a form of iatrogenic SAR that occurs after radical endonasal surgery, in particular after the resection of the nasal turbinates (lower and/or middle). Usually it is related to a nasal sinus surgery that modifies the physiological dynamics of the nasal air flow, slowing it down and reducing olfactory receptors activity.

It is characterized by nasal and pharyngeal dryness, paradoxical impairment of nasal respiration, dyspnea and hyposmia, and in some cases associated with depression.

14.2 Saddle Nose and Atrophic Rhinitis

The reconstruction of a saddle nose, derived from a chronic atrophic rhinitis, represents a tough challenge for surgeons.

The thick puckered skin of the nasal dorsum, in fact, is usually adherent to the underlying structures due to the chronic disease. It is difficult to elevate, and great care and patience is required to prevent buttonhole formation.

Rhinoplasty in atrophic rhinitis is a tailored and particular surgery because dorsal skin is different compared to the underlying strut.

Saddle nose deformity is defined as the depression caused by a decrease in the structural support of the cartilaginous and/or bony framework deep to the nasal soft tissue envelope [5]. The septum's articulation with the upper lateral cartilages of the nose and its contribution to tip support through the medial crura of the lower lateral cartilages play an integral part in the cause of the deformity and its correction.

On inspection, the saddle nose deformity may present with middle vault and dorsal depression, loss of tip support and definition, columellar retrusion, shortened vertical length, tip over rotation, and retrusion of the nasal spine and caudal septum.

The septal support test should be performed by applying force directly to the supratip area and evaluating collapse of the tip.

The term 'saddle nose' is used to describe a spectrum of severity of nasal deformities; therefore, surgeons need to adopt an analytical and diagnostic approach in planning the optimal reconstructive surgical strategy for each patient.

Saddle nose deformity can result in functional as well as aesthetic problems and both should be addressed at the time of surgery [6].

Saddle nose deformity comprehends a whole spectrum of conditions which may be classified according to several different classifications.

The Tardy classification, for example, divides saddle nose into minimal, moderate, and major deformities.

Minimal deformity involves a modest supratip depression and a mildly accentuated bony nasal hump.

Moderate saddling shows significant loss of quadrangular cartilage dorsal height, columellar retraction, and a broadened bony dorsum.

Major saddling is characterized by the same stigmata as the moderate deformities, with a higher grade of severity, and it is often associated with nasal twist.

Severe saddle noses are best corrected with a composite reconstruction technique, which involves restoration of the septal framework, in order to support the skin and soft tissue envelope and the nasal tip, followed by an aesthetic refinement aimed at the achievement of a better cosmetic outcome.

Another classification system was described by Daniel, which divides saddle nose into six types [7, 8]:

- Type 0 (Pseudo) saddle nose results from dorsal over-resection with strong septal support and a normal septal support test.
- Type I (Minor) saddle nose with a progressive loss of height of the cartilaginous dorsum.
- Type II (Moderate) saddle nose with further progression of the dorsal concavity and retraction of the columella.
- Type III (Major) saddle nose showing further dorsal collapse and loss of tip support. These patients often have a septal perforation.
- Type IV (Severe) saddle nose as a result of a larger septal perforation, with progressive loss of support in the lower half of the nose, a severely collapsed dorsum, loss of tip support, shortened nasal length, and contracture of the mucosal lining.
- Type V (Catastrophic) saddle nose with major lining, skin, and bony deformities that require major nasal reconstruction [9].

14.3 Main Reconstructive Techniques

The correction of saddle nose deformities is a reconstructive challenge. The septal saddle deformity can result from injury to the dorsal and caudal nasal septum of various nature. This may lead to a collapsed nasal dorsum and loss of columellar support, which result into under projection of the nasal tip. Optimizing aesthetic results requires not only to correct the depressed nasal dorsum but also to provide additional tip support, in order to re-establish the appropriate tip projection.

Furthermore, the atrophic rhinitis being a chronic process, the augmentation rhinoplasty in these patients is even more complicated than average, since the thick puckered skin of the nasal dorsum is usually tightly adherent to the underlying structures and it is difficult to be elevated. Moreover, great care and patience is required to prevent buttonhole formation.

Most cases of saddle nose deformity require the use of a large graft, in particular 'L'-shaped grafts are required in case of retracted columella. In augmentation rhinoplasty, the choice of graft material is a controversial topic.

Nasal reconstruction surgery relies in fact on the use of grafts, and the nature of graft materials has changed significantly during the last years. The characteristics of an ideal graft are well documented and include stability over time, malleability, adequate supply, low risk of donor site morbidity, low rate of extrusion, and low risk of triggering an immune/inflammatory response.

The types of implants currently available include a number of synthetic options and also homografts, but over time these materials are subject to complications such as infection, extrusion, and displacement [10]. Therefore, only the use of autografts is recommended in saddle nose reconstruction.

There are a number of different donor site possibilities including iliac crest and calvarial bone. In daily practice, the use of cartilage, especially septal one, if possible, is usually preferred. The septum does not require additional incisions and in addition the morbidity of the donor site is negligible, which makes it the best option.

Septal cartilage is easily mouldable and has good structural properties; moreover, there could be some indirect benefits linked to its use, such as the improvement of airway flow and the correction of a possible septal deviation.

The disadvantages of septal cartilage grafts comprehend the possibility of contour irregularities in thin skinned noses. There is also the potential risk of saddling after overly aggressive harvest of septal cartilage with subsequent loss of dorsal support. Furthermore, in case of atrophic rhinitis with a severe septal cartilage absorption, it is impossible to consider the nasal septum itself as a donor site.

In these cases, where septal cartilage results insufficient or unavailable, conchal cartilage might be used, though its natural curve and softness makes it not suitable to repair more severe deformities, whereas an extensive reconstruction requires more rigid grafts, such as costal cartilage ones.

The auricular concha grafts, however, are easy to shape and can be used to reconstruct the various components of nasal pyramid, since they provide adequate support and elasticity. The advantages of conchal cartilage grafts are similar to septal

ones. The harvesting of material is quick, easy, and low risk. They also show a negligible rate of resorption, with no reported cases of rejection.

On the other hand, it takes an additional incision and dissection to harvest conchal cartilage grafts and they may shift after the operation, causing asymmetry of the dorsum. The ribs are an abundant source of cartilage, also they are the preferred choice for the construction of a three-dimensional support [11]. Unfortunately, the costal cartilage graft tends to warp, which may cause distortion of the nasal form after surgery [12]. Further disadvantages are post-operative pain and the possible pneumothorax that will be a matter of discussion afterward.

Eventually, free diced cartilage (septal, auricular, or costal) ore wrapped in deep temporalis fascia is usually used to refine the aesthetic appearance over the new framework.

Before any kind of surgery is programmed, the patient's nose needs to be inspected both externally and internally.

External assessment includes palpation to assess the extent of residual septal support to the dorsum and tip—the "septal support test". Loss of normal resistance is a significant sign that implies septal reconstruction is likely to be required. Shortening of the nose and altered tip rotation should be noted at this stage. The bony pyramid should also be studied, as should the skin and soft tissue envelope (SSTE). A progressive loss of septal integrity results in a characteristic saddle nose deformity, with depression and splaying of the middle vault, loss of support and over-rotation of the tip, decreased vertical projection, retraction of the columella, and widening of the nasal base.

Thick skin may hide subtle irregularities that become evident after the reconstruction, as the skin does not drape well on the new rebuilt scaffold; therefore, a stronger reconstructive framework is needed to ensure a better final result. In contrast, thin skin usually better drapes over a reduced nasal profile, but the underlying grafts may become visible over time. Internal assessment with rigid endoscopes allows the assessment of septal deviation or perforation and the presence of synechiae between the septum and lateral nasal walls. From an anatomical perspective, there are four main parameters to consider when facing saddle nose reconstruction:

1. Lateral view nasal length:
   (a) The distance from the nasion to the subnasale (this is usually maintained in all but the most severe cases)
   (b) The nasion to columella break point
   (c) The nasion to the tip defining point
2. Dorsal projection (both bony and cartilaginous)
3. Tip projection
4. Tip rotation (disorders of this parameter usually result from altered nasal length)

Treatment of saddle nose deformity follows Daniel's classification, with minor deformities being treated with simpler techniques and major deformities requiring

more advanced reconstructive strategies. Less severe deformities with strong tip support may be easily camouflaged with dorsal onlay grafting using a variety of materials [13]. Types 0 and I can therefore be corrected with onlay grafts of cartilage or soft tissue or diced cartilage (free or in fascia).

Types II to V require structural solutions. Spreader grafts that are extended dorsally may be enough to fill in the dorsal concavity. Otherwise, a dorsal onlay graft can be placed on top of the structural foundation of the spreaders.

Five potential sources of grafts are commonly used: septum cartilage, auricular cartilage, iliac bone, calvarial bone, and rib cartilage.

14.3.1 Nasal Septum Cartilage

Type I and II saddle nose deformities are characterized by minimal loss of dorsal support, tip support, projection, columellar retraction, and nostril rounding. Composite septal cartilage-bone or conchal cartilage grafts. Those are ideal features for dorsal augmentation [14].

Minimal saddle nose can be corrected by restoring satisfactory septal height [15].

This group of patients have mild depression in the middle third (supratip), with good residual cartilaginous septal support dorsally and caudally, and a normal or near-normal lower third and tip position.

Generally, the nasal length is normal to the subnasale, but these patients may show a slight loss of tip projection and a low grade of retraction of the columella.

The external approach is the most suitable in these cases. The septum must be assessed to determine whether sufficient cartilage remains to allow the harvesting of a segment in order to generate a columellar strut graft or septal extension graft (SEG) [16].

The columellar strut graft is fashioned into a straight strut and it is positioned between the medial crura of the lower lateral cartilages and sutured, so that the posterior edge of the strut is anterosuperior to the anterior nasal spine (ANS). The septal extension graft (SEG) is sutured to the caudal edge of the septum in "overlapping" or "end-to-end" mode.

The strut prevents tip retro projection and it may also improve the projection.

The dorsal defect can be easily fixed with the supratip injection of diced cartilage (septal or conchal cartilage), which can be moulded to re-establish a normal dorsal profile.

In case of type I or II saddle nose, the diced cartilage can be used as free diced cartilage, free diced cartilage wrapped in fascia or fluid cartilage.

14.3.2 Auricolar Concha Cartilage

In **moderate saddle nose**, a linear profile cannot always be restored exclusively with use of septal cartilage, as the nasal septum is often absent or insufficient; therefore, the auricular cartilage offers a valid alternative [17]. It can be harvested almost entirely via an anterior approach, but a retroauricular one is also possible.

A vertical median-posterior incision is made and the posterior surface of the auricular concha is completely exposed. Four or five straight needles are then inserted into the anterior surface to map out the shape of the graft, leaving the antihelix fold and helix root intact. Hence, it is possible to cut the cartilage of the concha on the posterior surface with no risk of damaging the morphology of the auricular pavilion. A subperichondrial detachment of the anterior surface of the graft is then carried out to reach its complete isolation and to allow its safe removal.

The harvested conchal cartilage is then used to create tailored grafts that can be placed on top of each other according to the desired length and height.

These grafts are always inserted via an external approach and are sutured to avoid any displacement and secondary deformity. The curved shape of all the conchal cartilage makes it suitable for the correction of saddle nose deformities of various degrees, as various layers of cartilage can be sutured together depending on the scale of the deformity.

When it comes to the structural reconstruction of different anatomical components, the shaping of conchal cartilage can be far more complex.

Beforehand, it is mandatory to carefully plan and rationalize the different pieces that are to be obtained from the concha.

When saddle nose deformity is associated with decreased tip projection and/or modification of tip rotation, the dorsum augmentation procedure is completed by the placement of a columellar support that can be included in the previously described cartilaginous framework. Indeed, a simple augmentation effect on the dorsum does not resolve the deficient support of the base of the nose characterized by splayed nostrils, poor tip projection, and a short columella.

Given its particular robustness, the median border region between the cavum and the cymba of the auricular concha represents the best source to obtain columellar struts. Two spreader grafts can be obtained from the marginal region of the cavum or the cymba and then sutured to the sides of the dorsal septum, with the concave face towards the centre, in order to reconstruct the middle nasal vault and restore the inner nasal valve. When a subtotal reconstruction of the nasal septum is needed, a conchal graft can be attached to two spreader grafts obtained from the same concha in order to straighten its structure.

Saddle nose deformity is frequently associated with a dysfunctional internal nasal valve. In such cases, it is recommended the use of the so called “butterfly graft” that treats the internal nasal valve and also provides support to the external nasal valve through its effects on the scroll region, which are transmitted to the lower third of the nose [18]. The butterfly conchal graft is a graft that overlaps the distal half of the upper lateral cartilage (ULC) and rests under a small pocket created in the cephalic portion on the LLC (lower lateral cartilage). It is important to stress that this graft is positioned in the horizontal plane, whereas others are commonly placed in a sagittal plane [19]. In fact, the horizontal placement of this graft widens the internal nasal valve angle and provides support to the lateral alar crura, placed above it. This prevents the collapse of the external nasal valve as well (Figs. 14.1 and 14.2). When the butterfly graft is positioned properly, an improvement of the peak nasal inspiratory flow may be observed, proving its usefulness in repairing both nasal function and its aesthetics simultaneously. Several possible errors could be made during this procedure [20]. For example,

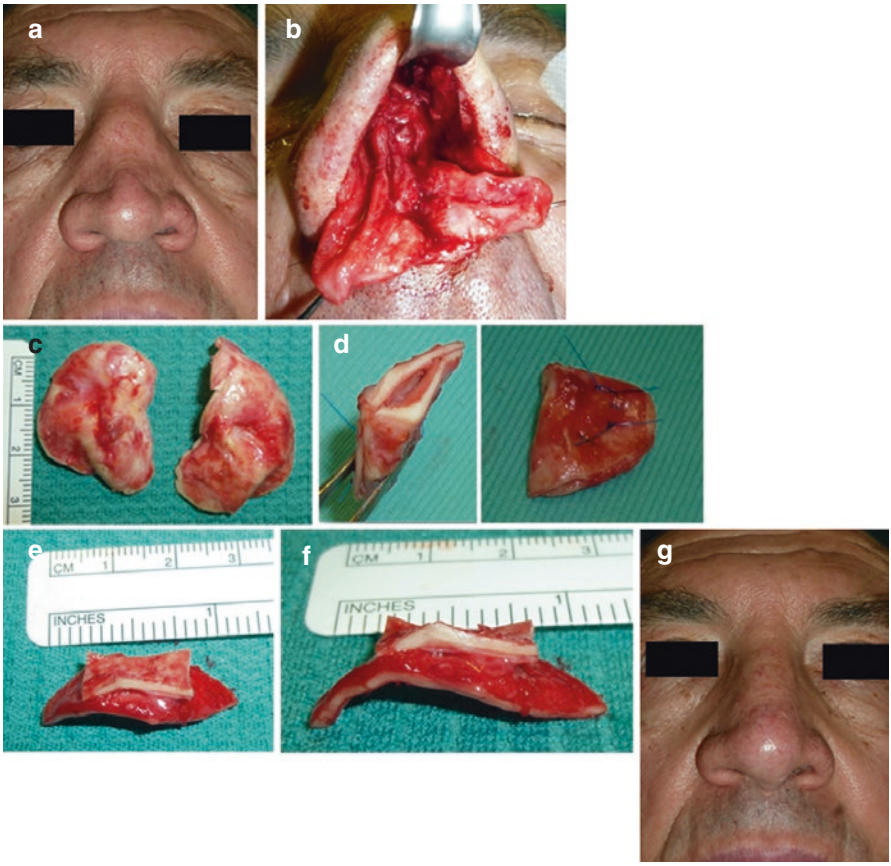

Fig. 14.1 Pre-operative (**a**) and 24-month post-operative (**g**) views of a man who presented the saddle nose deformity (type III) with a dysfunctional of the internal and external valve. Reconstruction L-strut with conchal grafts (**b**) septum has collapsed, pulling the upper lateral cartilage and splaying them (**c**) bilateral conchal grafts before shaping (**d**) caudal replacement graft shaped by concha (principle back-to-back cartilage graft) (**e**, **f**) conchal butterfly graft and onlay graft

the conchal cartilage graft might be too tight to be properly shaped into a suitable graft; the misplacement of the graft may also occur. Moreover, a graft positioned too high on the dorsum does not provide any improvement in breathing and it can also worsen the aesthetic of the nose.

In order to tackle complications, like the protrusion of the edges of the graft or the evidence of its irregularities from under the skin, different kind of materials can be used as cover. In 2012, Antohi et al. presented a technique for dorsal augmentation using a composite graft consisting of conchal cartilage and retroauricular fascia [21]. The autologous composite graft consists of pieces of conchal cartilage and retroauricular fascia harvested through the same incision in the retroauricular sulcus. The post-operative scar is inconspicuous and donor site morbidity is minimal. This chondrofascial graft is appropriate for slight-to-mild dorsal nasal augmentation but not for structural support.

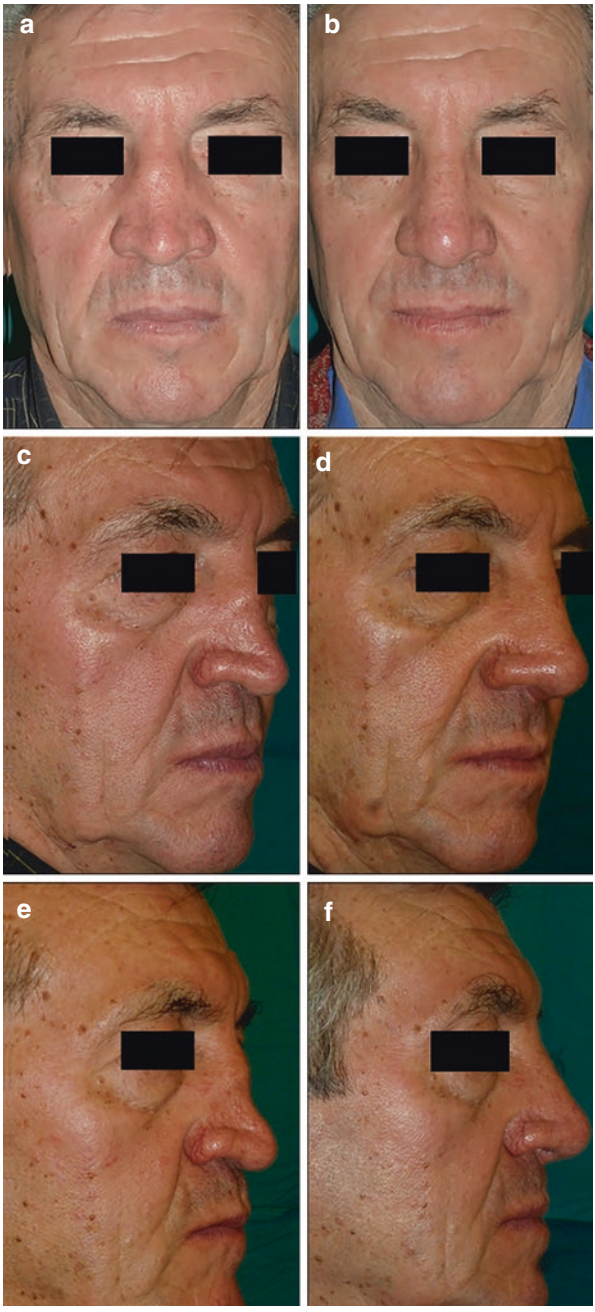

Fig. 14.2 Pre-operative (**a**, **c**, **e**) and 24-month post-operative (**b**, **d**, **f**) views of a man (same patient as in Fig. 14.1) who presented the saddle nose deformity (class III) with a dysfunctional of the internal and external valve. Reconstruction L-strut with conchal grafts (caudal replacement graft and butterfly graft)

In some cases, strips of cartilage can be obtained from the concha and joined together to form a single graft capable of correcting structural defects in various sections of the nose. The curved shape of the conchal cartilage has also been straightened out using incisions, sutures, or the superimposition of grafts.

In case of severe nasal dorsal collapse, structural auricular cartilage grafts may not be sufficient.

14.3.3 Calvarial Bone

Type III and IV saddle nose deformities usually require a more rigid structure, such as bone or rib, to provide support for the cartilaginous framework and envelope.

The L-shaped split with calvarial bone graft for nasal dorsal reconstruction of septal saddle nose deformities provides the following benefits: dorsal support, increased tip projection, improved nasal airflow, and a natural feel and appearance to the nose [22].

The procedure can be performed using the open rhinoplasty approach without the need for radix incisions for rigid fixation or intranasal incisions. In addition, graft donor site morbidity is kept to a minimum [23]. These advantages make the split calvaria bone L-shaped strut technique excellent for nasal reconstruction in patients with substantial septal saddle nose deformities.

On the other hand, when compared with the rib cartilage graft, the cantilevered calvarial bone graft anchored shows several problems [24].

For example, bone is more dependent on an adequate blood supply compared to cartilage and the process of harvesting and carving strips is more complicated. The process of cantilevering requires fairly thick bone in the radix to support the load at the tip of the nose and to accept the screws needed to affix it to the nasal bones.

Moreover, this added projection might not be tolerated in patients who already have a shallow radix.

Finally, the cantilevered graft makes it harder to precisely set the tip projection.

In case of complex reconstruction, the gold standard is the autologous rib cartilage as it can provide large amounts of strong and malleable tissue to be used for support and aesthetics.

In his study in 1990, Baser reported that though the immediate results of autologous cancellous bone graft were excellent, on a longer follow-up they proved to be highly unreliable. Despite securing firm adherence with the underlying bone, the rate of absorption seemed to be unusually high in atrophic rhinitis patients.

14.3.4 Rib Cartilage

Patients suffering from atrophic rhinitis often need rib cartilage during a reconstructive rhinoplasty, since the septal cartilage is either structurally inadequate or already missing. When costal cartilage is used, a structural dorsal graft can be placed to span the nasal bones to the caudal septal support. Structural dorsal grafts can be

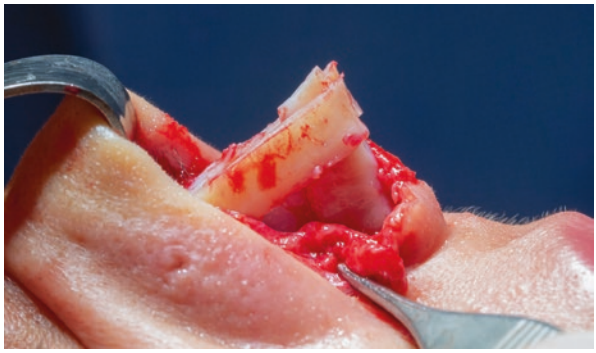

Fig. 14.3 The L-strut fashioned of rib segment is performed (bilaterally extended spreader grafts and caudal replacement graft)

integrated into caudal septal extension or into replacement grafts to recreate the L-strut support of the nose (Fig. 14.3).

Grafts harvested from ribs cartilage are considerably versatile in shape, length, and width [25]. Long and straight struts can be prepared from the rib cartilage to reinforce or to reconstruct the nasal pyramid. This facilitates nose reconstruction in all types of functional and aesthetic pathologies.

However, the use of rib cartilage grafts has several drawbacks, as primarily it implies an additional incision located far from the nose. Fortunately, the resulting scar is relatively short (about three centimetres) and it is generally not very evident in women since it is placed in the inframammary sulcus.

Further disadvantages are post-operative pain, possible pneumothorax and the potential risk of graft warping. This last one, due to the stress applied to the graft, represents a long-term (post-surgery) shape alteration of the nose. Warping can be avoided by means of different techniques which can be applied during the carving of the graft and during the nasal surgery, like internal stabilisation, "rasping nasal bone", DCF, Kirschner wire through the length of the dorsal graft, cartilage dissection, chimeric grafts, etc. [26].

Rib cartilage is less calcified and more elastic in young individuals and this allows the preparation of thin grafts for alar cartilage reconstruction.

It is to be preferred a 3–3.5 cm inframammary incision in female irrespective of which rib is underlying. Usually, cartilage is harvested from the sixth or seventh rib, depending on the rib that is the longest and straightest [27]. After the incision of the skin and subcutaneous tissues below Scarpa's fascia, the fascia of the rectus abdominis muscle is reached and a piece of approximately 4 × 4 cm of it is harvested. Subsequently, muscle fibres are spread along their axis rather than transected (split longitudinally), and a full thickness piece of rib of appropriate length is harvested circumferentially with a perichondral strip attached anteriorly and leaving perichondrium below. A precise surgical technique that avoids muscle section minimizes post-operative pain. Around 3–4 cm of the rib segment is considered to be sufficient for any deformity [28] (Fig. 14.4).

After the rib cartilage has been harvested, the donor site is checked to ensure that no pneumothorax has occurred. The wound is filled with saline solution while the

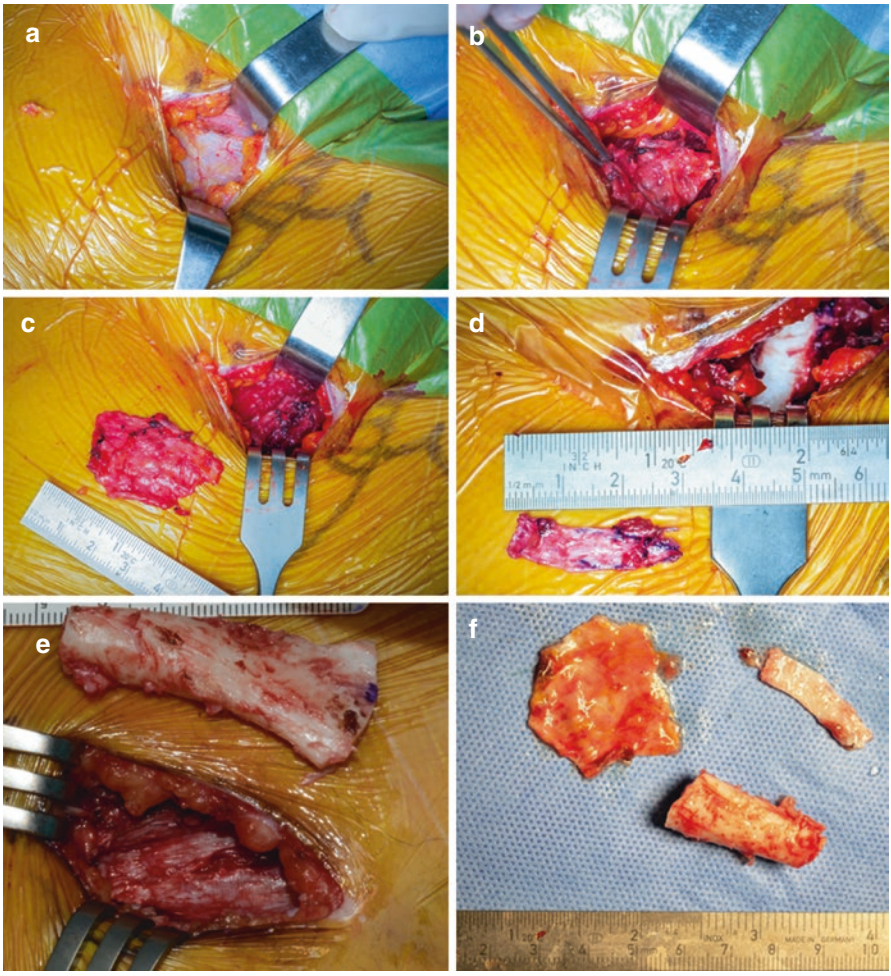

Fig. 14.4 Rectus muscle fascia (**a**, **b**, **c**) with perichondrium (**d**) harvest rib cartilage (**e**); all grafts harvested (**f**)

anaesthesiologist applies positive pressure into the lungs. If no air leak is detected, a pneumothorax can be excluded.

On the contrary, when a pneumothorax occurs, the injury usually involves only the parietal layer of the pleura and not the lung parenchyma; therefore, a chest tube is not needed [29]. Anyway, a catheter can be inserted through the parietal pleural tear into the thoracic cavity. The incision should then be closed in layers around the catheter. Positive pressure is then applied and the catheter is clamped until its removal in suction at the end of the operation [30].

The following step consists in rib "lamination", multiple segments of rib are precisely sliced longitudinally or obliquely, depending on the rib shape, in order to obtain pieces of different thicknesses. These multiple slices are then

Fig. 14.5 Concentric carving to decrease warping of costal cartilage graft. Rib cartilage provides the grafts with considerable versatility with respect of the shape, length, and width. Easily harvesting of the perichondrium and rectus muscle fascia

immersed in saline solution until needed. It is well known in the literature that warping usually takes place within half an hour after carving [31]. It is easy therefore to detect if the cartilage will have a tendency to bend and in which direction. Based on this feedback, further shaping of the cartilage can accommodate the natural properties of the rib. There are numerous methods to minimize warping of the costal cartilage graft. It has been suggested that centrally carved grafts exhibit a decreased rate of warping compared with peripherally carved ones (Fig. 14.5).

Another interesting method, is the so-called oblique split method proposed by E. Tastan [32]. A cross-sectional graft obtained through 30° oblique cut to the long axis of the rib results in a graft with equal circumferential forces of contracture that have a decreased chance of warping.

The oblique split method provides straight costal cartilage grafts of several thicknesses. In a review, Wilson et al. found that oblique split method yielded results comparable to concentric carving [33].

According to need, straight segments can be used, or convex ones, which may be employed in a juxtaposed configuration.

When well planned, executed, and dimensioned, rib grafting provides a proper structure without excessive bulk.

The open rhinoplasty approach provides better visualization without distortion of cartilages, leading to a more accurate diagnosis and treatment.

Septal mucosal flaps are elevated in a standard fashion and the cartilage remnants are exposed. Depending on the presence of a caudal or dorsal cartilage strip, the remaining framework may be reinforced or rebuilt with a segmental reconstruction graft. Segmental reconstruction enables the fine adjustment of the height and length of the new septum.

Different surgical techniques are available, Daniel R.K. et al. proposed the one based on the most significant case histories [34].

Here follows the technique used in the reconstruction of **type IV** saddle noses, namely the cases where the septal support is lost at the vault level (both bony and cartilaginous) and where there is a contraction of the lining tissues. In these cases, Rollin's technique is based on the setting up of the "L-strut" graft.

The L-strut graft is composed by a spreaders graft (a complete dorsal graft) and columellar strut graft. The upper part of the spreader graft is anchored to the "keystone area" or nasal bones area and its lower part is fixed to a columellar strut graft which is attached to the anterior nasal spine.

To maximize stability and avoid asymmetries, the caudal septal extension graft should be stabilized to the existing caudal septum with bilateral spreader grafts. Then medial crura are fixed to the caudal margin of the septal extension graft with "tongue-in-grove" sutures to achieve the desired tip projection and rotation. Osteotomies are performed if necessary.

Once a rigid structure has been established, the aesthetic contour can be created. After the stabilisation of the tip, it is hereinafter possible to restore the appropriate dorsal height using a diced cartilage graft wrapped in fascia. Rib cartilage is diced into tiny pieces. Composite reconstruction offers a unique solution to saddle nose deformity, as it is a flexible method of restoring structural support and aesthetic contour (Fig. 14.6).

The majority of saddle noses are corrected using a dorsal graft that is cantilevered cephalically on the bony vault with either apposition or support caudally from a columellar strut. Composite reconstructions provide both stability and aesthetic contour for the nose. The structure is in fact granted by the deep foundation layer, which provides a rigid framework on which a more superficial and malleable layer is set, resulting in a better aesthetic contour (Fig. 14.7). Thanks to this difference between the deeper and more superficial layers of the reconstruction, warping and malalignment are no longer an issue, as the major structural grafts are placed in a nonvisible location (Fig. 14.8).

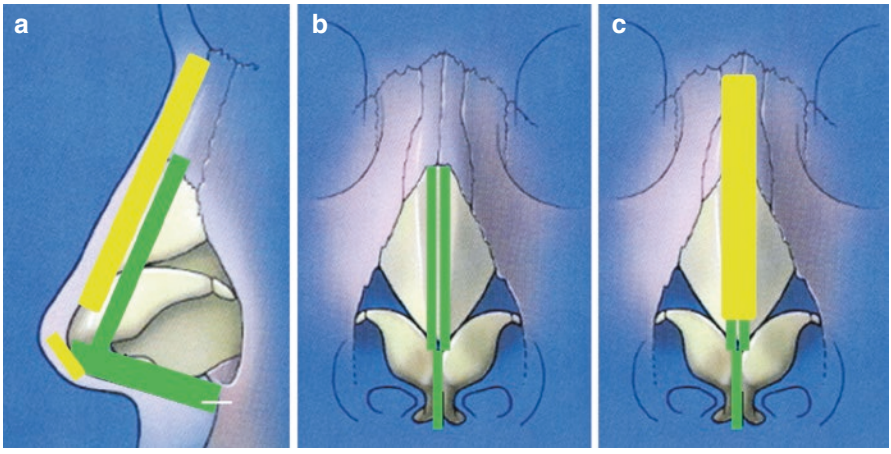

Fig. 14.6 (**a**, **b**, **c**) The concept of composite reconstruction of the saddle nose (type III and IV) presented in which a deep foundation layer for septal support is restored first and the a more superficial aesthetic contour layer is added

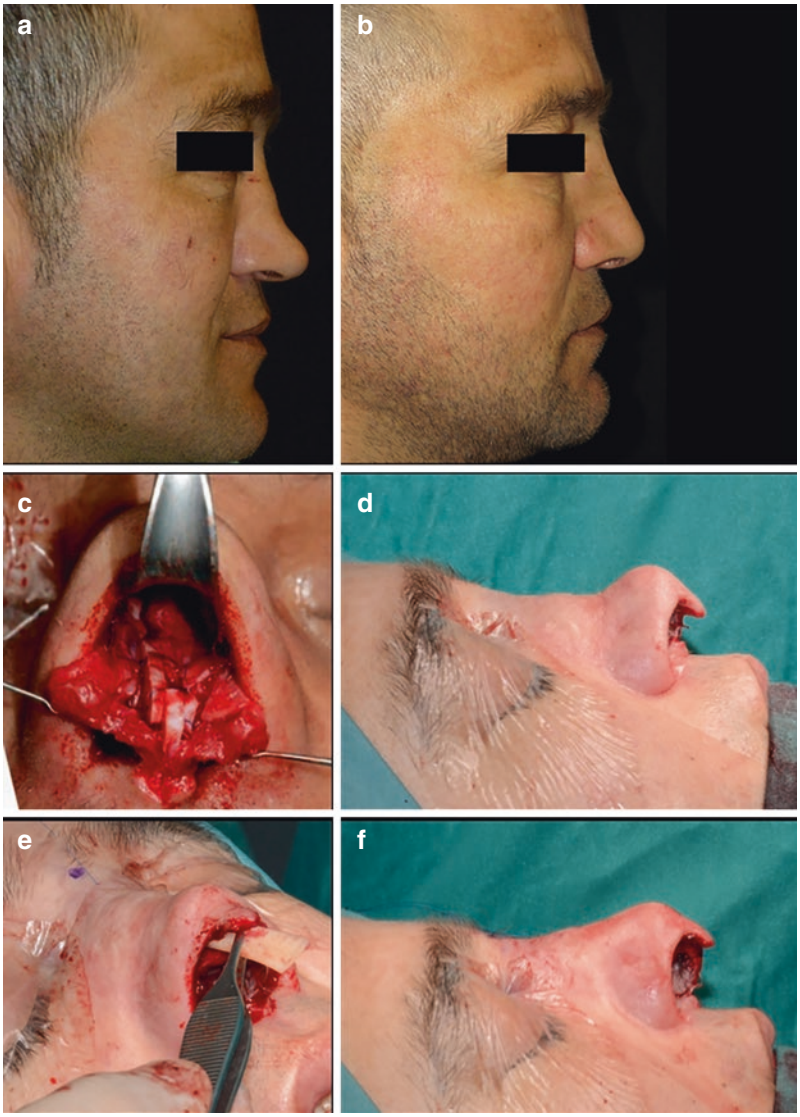

Fig. 14.7 Pre-operative (**a**) and 18-month post-operative (**b**) views of a man who presented the saddle nose deformity (type IV). Composite reconstruction with rib grafts. (**c**, **d**) Reconstruction of L-strut: bilaterally extended spreader grafts fixed at septal extension graft. (**e**, **f**) A thin longitudinal onlay graft is placed on the nasal dorsum. (**g**, **h**) The DCF (diced cartilage fascia) is used for final remodelling of the dorsum. The DCF is prepared using rectus abdominis fascia and rib cartilage

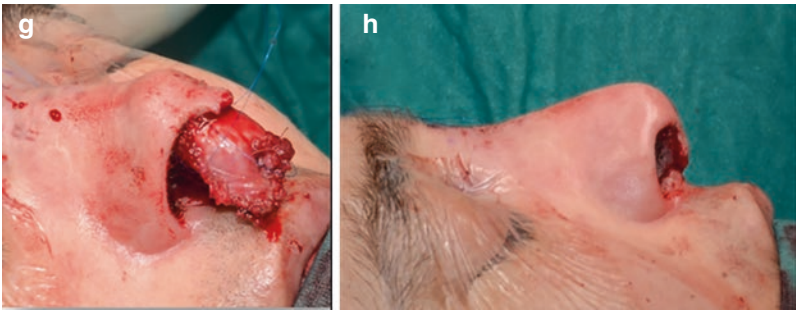

Fig. 14.7 (continued)

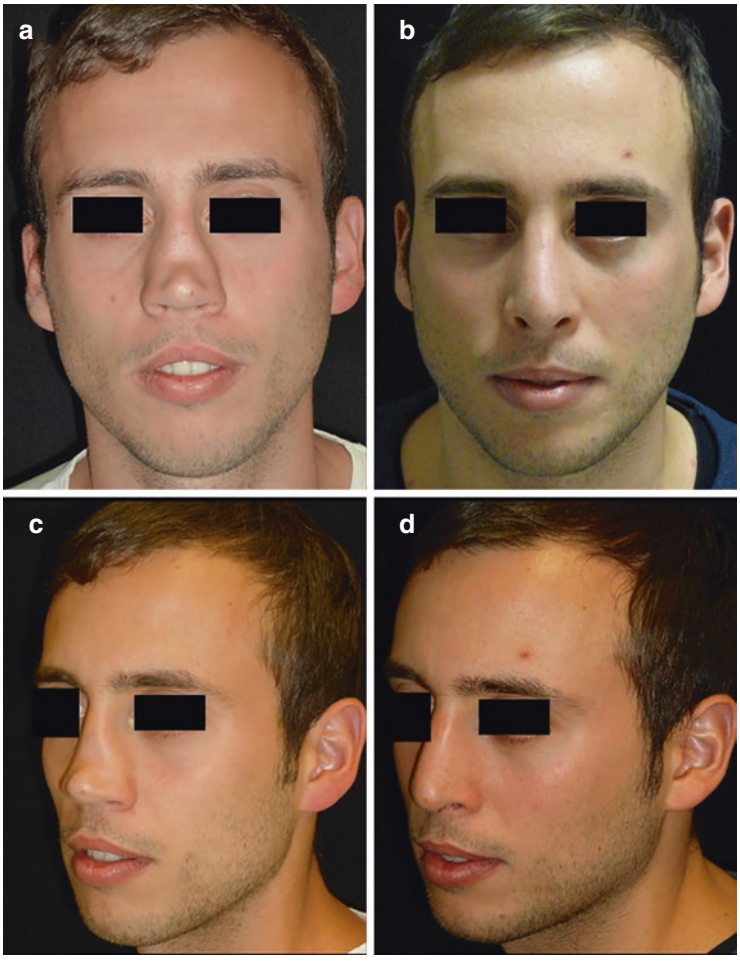

Fig. 14.8 Pre-operative (**a**, **c**, **e**) and 24-month post-operative (**b**, **d**, **f**) views of a man who presented the saddle nose deformity (type IV). Composite reconstruction has been performed with rib grafts

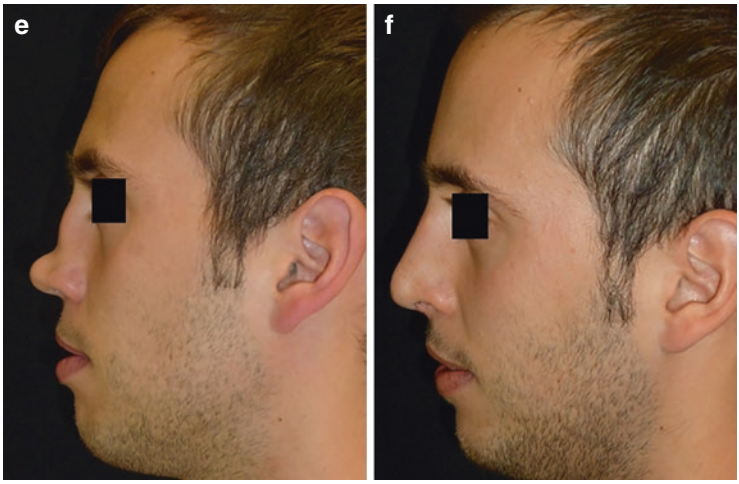

Fig. 14.8 (continued)

14.3.5 Diced Cartilage in Fascia (DCF)

Usually, solid dorsal onlay grafts are associated with high rates of revision because of various problems such as distortion, dislocation, palpability, and visibility, especially in thin skin. For this reason, diced cartilage grafts wrapped in fascia have become more and more popular in recent decades.

Many variants of the original technique firstly described by Erol have been published in the literature [35]. These techniques are different in the source of the diced cartilage (septum, concha, or rib) and in the type of the material that is filled with the diced cartilage. The cartilage is sharply cut to small pieces less than 0.5 mm in size, which ensures viability of the chondrocytes. The cartilage is not crushed, bruised, or morselized, which would lead to unpredictable survival. Over a period of months, the diced cartilage solidifies, and the survival rate is comparable to that solid grafts.

Initially, synthetic materials, such as Surgiderm or Alloderm, were proposed to build the sleeve, but they have been abandoned due to the loss of the diced cartilage following the inflammatory response induced by the foreign body resorption.

The use a DCF (diced cartilage in fascia) grafts has become a valid alternative in the final remodelling of the nasal dorsum as well as in the moderate augmentation procedures, according to the principles described by Daniel and others [36]. Temporal fascia is a good alternative, but it requires a second operative field and it is associated with a risk of alopecia and hematoma.

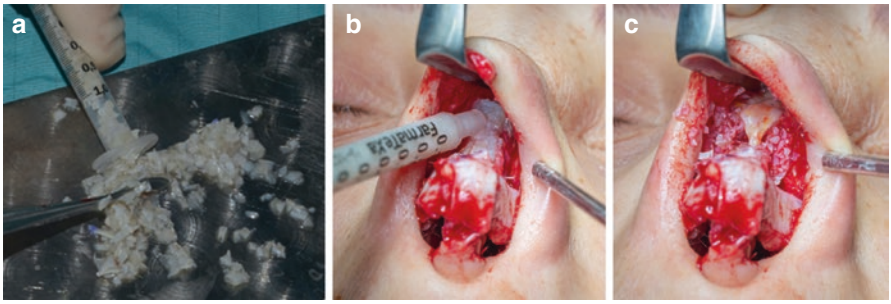

Fig. 14.9 Diced cartilage (DC) free from rib cartilage and septum is prepared (**a**) and placed on the dorsum with a tuberculin syringe for a minimal augmentation (**b**, **c**)

Diced conchal cartilage wrapped in the temporal or retroauricular fascia is an excellent combination and a simple and safe alternative for dorsal augmentation, especially in those cases where the defect is not too severe and there is no need for more cartilage for other purposes (tip, columella, etc.) [37]. In case of small defects "free" diced cartilage can be used. Following augmentation with DC, the recipient site creates additional fibrous tissue surrounding the graft, thereby creating a large semirigid graft. It is important that the surgeon does not "overgraft" as there is no post-operative absorption.

Diced cartilage graft is created by cutting cartilage, from any donor site, into 0.5-mm pieces. It is then inserted precisely into areas that need augmentation using a spatula-shaped instrument or injected with a tuberculin syringe directly into nasal dorsum (Fig. 14.9).

In patients who have severe saddle nose deformity, a composite reconstruction with autologous rib and DC, wrapped or not in rectus muscle fascia, provides the best result. The use of rib DC wrapped with rectus muscle fascia is a feasible option, in fact rectus muscle fascia grafts are associated with shorter operative times and they eliminate the need for an additional autologous donor site for the fascial sleeve [38]. Using this technique, structural reconstruction and cartilage vault restoration are accomplished using rib grafts. Following that, the DCF is inserted to create the aesthetic dorsal contour on top of the rigid underlying framework. The DCF is a full-length construct from the radix to the septal angle, precisely measured on the nasal dorsum in the required length and width, so that it has the specific desired distance between the nasofrontal angle and the start of the supratip break. Fixation points are two transcutaneous sutures at the radix and one at the supratip break. Usual measurements are 3 cm in length and 0.9 cm in width.

In the end, DCF provides a moderate augmentation so as to establish the final dorsal height prior to finalizing the tip [39]. However, the proper structure of the dorsal plateau below needs to be previously secured by prior L-strut reconstruction/stabilization and associated spreaders/extended spreaders on either side. Another alternative in certain situations is the use of rib perichondrium or fluid cartilage or DCF combined with thin rib longitudinal onlay grafts.

14.3.6 Fluid Cartilage and Lipofilling

Autologous fluid cartilage obtained from shaving the septal cartilage provides an autologous source of filler, and it has been demonstrated to be effective in the treatment of nasal dorsum and alar cartilage defects, or the correction of supratip imperfections. Moreover, the incomparable biocompatibility enables shaved cartilage to be a promising autologous biotechnology for tissue engineering. Another donor site can be the rib cartilage or the auricular concha cartilage, but with different peculiarities than those of the nasal cartilage.

The injection of saline solution loaded with shaved fluid cartilage into the defect site is highly desirable for cartilage repair or for the correction of nose defects; in particular, the use of fluid cartilage represents a flexible microinvasive procedure to fill the lesions.

This fluid graft can be applied to each section of the nose, including the dorsum, radix, nasal tip, premaxilla, alar base, columella, soft triangle, and more.

The injection should be performed at a deep level, in a tight space in contact with the cartilage or bone, without undermining the skin flap, in order to make sure that the graft is fixed in its place and to prevent any risk of dislocation.

Trivisonno et al. in a recent study of fluid cartilage described the capability of chondrocytes to survive for long periods after the injection and their angiogenic properties that actively contribute to the regeneration of tissues [40]. In conclusion, chondrocytes and fluid cartilage may be an interesting and possibly significant source of autologous tissue, which is ready to be used in therapeutic procedures, such as the regeneration or repair of nose tissue defects and irregularities. The use of fluid cartilage as filler may recover the quality of the nasal dorsum skin, improving the final aesthetic results of the rhinoplasty.

Another very interesting procedure is **lipofilling**.

In fact, the use of an autologous fat tissue graft in the nasal pyramid, though relatively uncommon, represents a particularly interesting tool for patients suffering from atrophic rhinitis, who usually have very thin skin [41].

One of the main characteristics of lipofilling is the presence of high levels of mesenchymal stem cells able to regenerate the tissues. This property has been particularly useful in the treatment of numerous pathologies such as radiodermatitis, burn sequelae, chronic ulcerations, and anti-ageing therapy.

Therefore, lipofilling is an interesting tool for the augmentation and the improvement of nasal dorsum skin quality. Given its volumetric qualities and its action on cutaneous trophicity, adipose tissue can be considered the best filler.

Nevertheless, it is essential to understand that stable nasal modelling is obtained through the reshaping of architectural elements as bone and cartilage, leaving soft tissues to adapt to changes and draw the final result. Autologous fat grafting applied to nasal aesthetics works oppositely by altering only soft tissues to mask architectural imbalances or irregularities except when it is used in combination with rhinoplasty to supplement deficient bone in the radix, glabella, and premaxillary region. In these later cases, fat grafting has worked with the same efficacy as cartilage grafts or solid prostheses in the same locations [42].

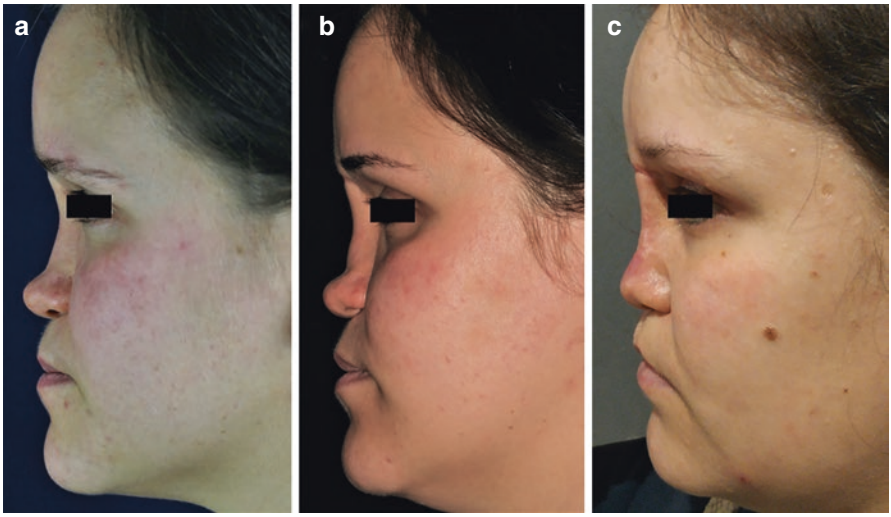

Fig. 14.10 Pre-operative stage of 25-year-old woman with a saddle nose deformity (type IV) (**a**); (**b**) 6-month post-operative result after the last lipofilling injection. Overall two lipofilling sessions have been done (the second done after 6 months after the first session). (**c**) 6-month post-operative phase (lateral views) after composite reconstruction with rib grafts. In childhood, the patient had undergone nasal radiotherapy treatment. The very thin skin was adherent to the underlying structure. Fat graft technique has improved quality of skin making rhinoplasty easier. Composite reconstruction has been performed with rib graft

These observations are primarily important in patients with atrophic rhinitis because they have very thin skin, adherent to the bony and cartilaginous planes. The use of fat tissue grafts to treat saddle nose could be the first choice in some selected cases with a high degree of scarring or adherence. Fat tissue grafts, in fact, have demonstrated the ability to loosen tightly adherent skin in a way that improves the outcome of rhinoplasty in patients with atrophic rhinitis. The high level of mesenchymyl stem cells contained in adipose tissue endows them with regenerative properties.

In case of patients with a mild or severe saddle nose deformity, secondary to atrophic rhinitis, a series of two session of microinjections of fat tissue grafts on the dorsum can be performed 6 months before the augmentation rhinoplasty, in order to obtain a better quality of the skin (Fig. 14.10).

The possibility of a second lipofilling session must be envisaged, since fat tissue tends to be resorbed weeks after the procedure.

14.4 Conclusion

Atrophic rhinitis is a chronic, gradually progressing degenerative condition of the nasal cavity. Worsening of the metaplasia and atrophy of all mucosal components (epithelium, vessels, and glands) takes place because of increased osteoclastic activity, resulting in a volumetric decrease of nasal structures.

Progressive loss of septal integrity results in a characteristic saddle nose deformity with depression and splaying of the middle vault, loss of support and overrotation of the tip, decreased vertical projection, retraction of the columella, and widening of the nasal base. Functionally, the internal and external valve are affected, leading to significant difficulties in breathing. Rhinoplasty in atrophic rhinitis is a difficult surgery because the dorsal skin is thin and strongly adherent to the underlying structures.

Dorsal augmentation is primary important to shape an ideal nose.

The therapeutic management of saddle nose has always been a surgical challenge.

The first element of discussion concerns the reconstruction materials used to correct saddle nose. The most common is cartilage derived from various sites depending on the shape and number of grafts required: septum, concha, or rib. Cartilage is an easily harvested material that can be modelled to form fine, anatomical grafts to correct superficial irregularities or very large grafts to fill large defects [43].

The treatment strategy proposed here is based on a classification that is designed to be as practical as possible and which allows progressive and adapted therapeutic management.

Rib cartilage continues to be the preferred grafting material for complex rhinoplasty deformities when a considerable amount of cartilage is required for dorsal augmentation and/or to strengthen structural integrity. Despite improvements in harvesting and processing of rib cartilage (such as a balanced cross-sectional carving), the primary critical issues of solid rib cartilage remain: visibility, abnormal contouring, and warping. Wrapping diced rib cartilage in autologous fascia addresses these limitations by providing a pliable dorsal graft with minimal visibility and a smooth transition between dorsum and lateral nasal subunits, without the risk of warping.

Injection of autologous fat tissue is an interesting tool to improve nasal dorsum skin quality, especially if it is thin and cicatricial, before rhinoplasty.

To correct a saddle nose is a tailored surgery and not a just a fixed step-by-step technique.

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Surgical Treatment of Atrophic Rhinitis: Use of Autologous Costal Cartilage Grafts

15

Fazil Apaydin

15.1 Introduction

Costal cartilage is one of the main sources for grafts in the reconstruction of saddle nose deformities and revision rhinoplasty cases. However, its handling and carving methods have always created a challenge for surgeons. In 1958, Gibson and Davis published a technique called "principle of the balanced cross-section" which could be used to overcome warping, the major disadvantage of the use of carved/sculpted costal cartilage [1]. They stated that if the distorting forces were balanced along a cartilage graft, the grafts would not be distorted (warp). In total, 46 balanced cross-section grafts were followed for over a 3-year period. Later, Tastan et al. proposed the oblique split method, describing the angle to the long axis of the rib cartilage upon which the costal cartilage is cut/sectioned. In this original description, there was no clinical observation of graft warping in the follow-up period [2]. It was also stated that although the grafts obtained could be modified into different shapes, they preserved their straight shape.

15.2 Costal Cartilage Sculpting Methods

15.2.1 The Principle of the Balanced Cross-Section

This principle is still the fundamental technique when costal cartilage use comes into consideration in saddle nose corrections or revision rhinoplasties [1]. The sculpted cartilage grafts are used as structural grafts and augmentation grafts. Besides, the integrated dorsal graft/columellar strut has been used in many cases, where the caudal septal support was poor [3]. It has been reported that careful

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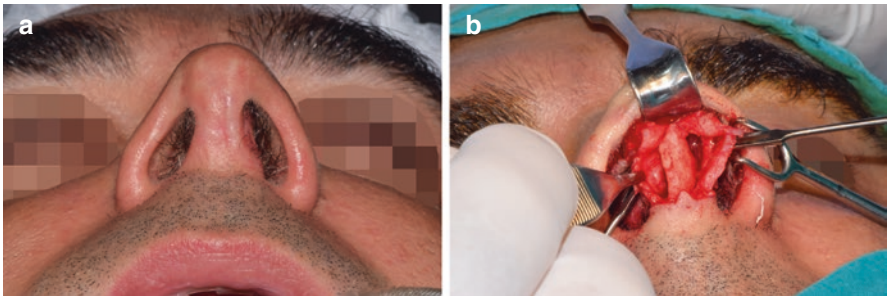

Fig. 15.1 In the reconstruction of crooked nose, a subtotal reconstruction was done by L-strut obtained from the sixth rib. It was warped (**a**) and a revision was needed (**b**)

symmetric carving of costal cartilage could minimize the chance of cartilage warping over time [3]. Our experience has shown us that costal cartilage warping can still occur despite careful symmetric carving, especially while using structural grafts (Fig. 15.1). The one-piece L-strut graft obtained from the costal cartilage was described by Rettinger and its use has been effective for decades [4]. Our experience of dorsal onlay grafts is that they rarely have clinically apparent warping. However, warping has remained the primary concern with the use of costal cartilage grafts. Many cutting and additional techniques have been developed to overcome this issue. For the last 19 years, we have been utilizing balanced cross-sectional carving, and although warping was rarely seen, concerns always remained. The use of thicker grafts employed by us and other experienced rhinoplasty surgeons to minimize warping resulted in stiffer noses, which was undesirable to some patients.

Freehand carving/sculpting of costal cartilage with a scalpel has historically been the technique of choice for fashioning grafts. The creation of thin grafts using this technique is however technically challenging and carries a higher risk of warping. Dermatome blades overcome the technical challenges of producing thin grafts, however the unfavorable warping characteristics remain [5].

An observed major limitation was the paucity of grafts that can be obtained by this method.

The central portion of the rib is utilized as a graft, with the remaining peripheral cartilages portions/shavings often unusable due to the unfavorable warping characteristics. Typically, in the correction of saddle nose deformity, we use the central rib portion as a caudal septal graft and the one outer layer/shaving is used as a dorsal onlay graft. However, in revision rhinoplasties, variation in graft type, size, and amount of graft material required limits the use of balanced cross-section carving rib carving.

15.2.2 Oblique Split Method

I have learned this technique during a meeting from Dr. Tastan in 2008, several years prior to its publication [2]. Impressed with the simple logical solution to this

common and difficult problem, I adopted his technique. My preferred ribs have been the fifth and the sixth due to the ease of access through the inframammary incision in females. After harvesting the 4–6-cm-long rib, the cutting angles, direction, and the length of the implants are calculated dependent on the requirements. The idea is to obtain the longest possible implants depending on the shape of the harvested cartilage (Fig. 15.2).

What kind of instruments have I used throughout the past 10 years? I started using the microtomes of the pathologists. They were longer than a scalpel and very helpful to make clean long cuts and obtain smooth grafts. After cutting my fingers a few times, I found a microtome handle which kept my fingers on the safe side. Then I used dermatome blades which further improved sectioning the rib cartilage. Almost 4 years ago, I found the ideal blade which I call as Chef's knife [6]. While working with the costal cartilage, I always looked for a knife with the cutting height of at least 7–8 mm, which is usually the height of the rib. The blades are 13 cm in length and 14 mm in height. When placed in the blade holder, its cutting height becomes 8 mm (Fig. 15.3). With the help of this knife, the cuts can be done more precisely with improved control and 0.5, 1, 2, and 3 mm thick grafts can be obtained. In the majority of the cases, the outer cortex is left intact which helps stability and prevent warping and absorption.

Fig. 15.2 The sixth costal cartilage is obtained and markings are done to decide on the best way for oblique cuts (**a**). The Chef's knife is used for precise cuts (**b**). As seen in the picture, about 12 implants of various thicknesses with the preserved outer cortex are obtained and more implants can be sculpted from the remaining cartilage (**c**)

Fig. 15.3 The Chef's knife is composed of two parts: A 26 cm blade holder and a 13 cm blade (**a**). The blade is inserted in the housing of the holder and a bolt is used to fix the blade in place. The microtome blade is put on the ruler for comparing the dimensions of both blades (**b**)

15.3 Clinical Situations to Use Costal Cartilage

15.3.1 Nasal Septum

Nasal septum can be severely deviated, or partially absent especially in saddle nose, congenital disorders such as Binder's syndrome or cleft lip nose. The severe deviation can be traumatic or iatrogenic due to previous surgery. In these situations, there is a need for straight implants to reconstruct the nasal septum. The nasal septum can be divided into imaginary sections, and these grafts can be used to reinforce or replace each of the segments (dorsal and/or caudal) to obtain a straight L-strut. In cases of previous septal abscess where all the septal cartilage is deficient, it is possible to reconstruct the entire septal cartilage by using the grafts obtained with an oblique cutting technique. Instead of using a template such as PDS foil, these implants of 1–2 mm in thickness can be sutured on 0.5-mm-thick implants. The dorsal segment can be supported from both sides by splinting spreader grafts, then they can be coupled with a caudal septal extension or replacement graft (Fig. 15.4).

15.3.2 Saddle Nose

In saddle noses, there are two main issues to address: the nasal septum and the need for augmentation. Regarding the septum, the techniques are described above. For dorsal augmentation, I have been using the following techniques:

- Solid onlay grafting
- Laminated grafts
- Diced cartilage in fascia [7, 8]
- Cartilage chips in fascia

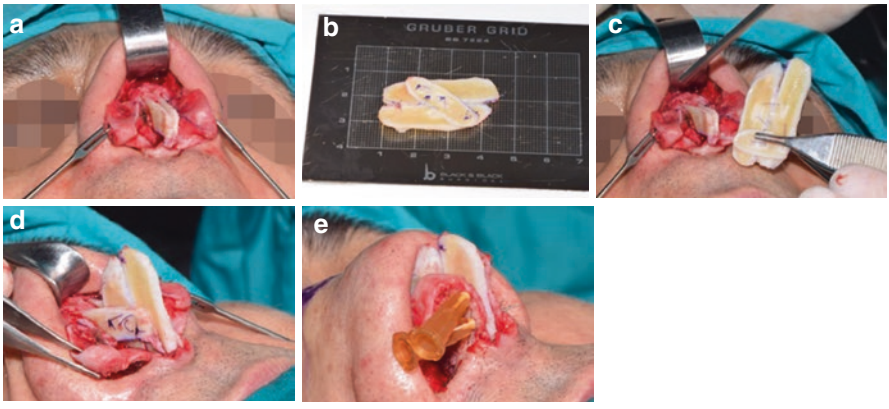

Fig. 15.4 Two splinting spreader grafts are sutured to the small piece of septal cartilage at the key area (**a**). A new septum is constructed by bringing two 2-mm-thick implants sutured to each other by 0.5 mm thick graft (**b**, **c**). The new septum is sutured to the spreader grafts to rebuild the L-strut (**d**). The medial crura are sutured to the new septum as a tongue-in-groove (**e**)

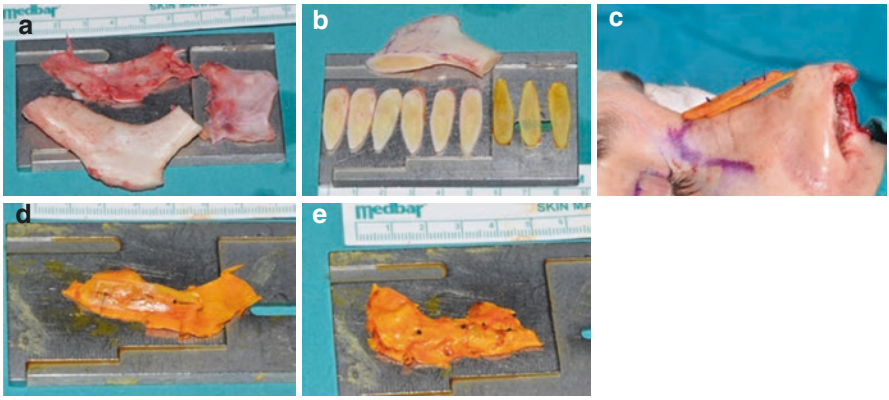

Fig. 15.5 The sixth rib harvested with rectus abdominis fascia and the outer perichondrium (**a**). Multiple implants of various thicknesses are cut by oblique split (**b**). Two laminas are sutured together for augmentation (**c**). The dorsal surface and the lateral parts of the implants are covered by perichondrium for camouflage (**d**, **e**)

The laminated graft technique involves the combining of two or more obliquely cut grafts by suturing. They are tailored to the needs of the augmentation by partial shaving. I like covering the upper part by means of perichondrium obtained from the outer surface of the rib (Fig. 15.5). The advantage of this technique is that many oblique cut grafts can be brought together to get the desired dimensions with no risk of warping and resorption.

15.3.3 Revision Rhinoplasty

The patients usually seek revision surgery due to over-resection, under-resection or persistent nasal deviation. In cases of over-resection, graft requirements can often exceed the amounts of cartilage that can be harvested from conchal cartilages. In these situations, the oblique split technique has provided large amounts of straight grafts of various thicknesses and lengths from a single rib, while avoiding technically complicated and time-consuming carving techniques. The volume and the variability grafts that can be produced combined with the speed of the oblique split method provide the surgeon greater flexibility than other methods. I have had a chance to cut paper-thin implants to use as lateral crural strut grafts, camouflage grafts (Fig. 15.6). In younger patients, the thinner implants can easily be bent to reconstruct the lower lateral cartilages (Fig. 15.7). These thinner grafts avoid rigidity and stiffness associated with the use of the thicker grafts.

15.3.4 Atrophic Rhinitis

An accepted treatment modality for atrophic rhinitis is to narrow the nasal passages by inserting cartilaginous grafts under the inferior turbinates [9]. The use of rib

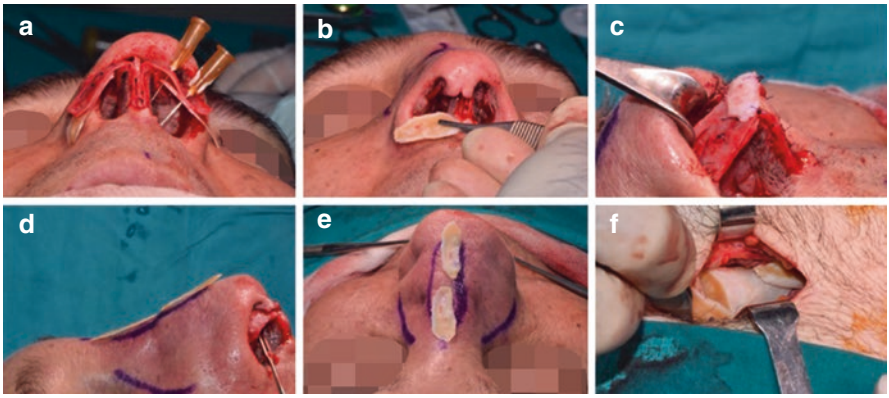

Fig. 15.6 When thinner implants are used as lateral crural strut grafts, the patients do not palpate them from inside (**a**). A similar situation is valid for alar batten grafts as well (**b**). Tip grafts can easily be carved from rib cartilage (**c**). Paper-thin implants can be used for camouflage purposes (**d**, **e**). The remaining cartilages can be inserted into the recipient bed for support (**f**)

Fig. 15.7 In younger patients, the thin implants are flexible enough to reconstruct the missing lower lateral cartilages partially or totally. In this case, the lateral crura and the domes are reconstructed by thin rib implants (**a**, **b**). Then, a shield graft is sculpted for a better tip definition and projection (**c**)

cartilage in the treatment of atrophic rhinitis has been described in the literature [10–12]. The grafts obtained from the rib cartilage by oblique split technique can easily be used for the treatment of atrophic rhinitis, while it has many advantages in comparison to other sculpting techniques.

15.4 Conclusions

There are two main types of costal cartilage sculpting: symmetrically balanced cross-section and oblique split method. The author's clinical experience over the past decade has demonstrated the superiority of the oblique split method in terms of graft material and reduction in clinical significant warping. That is why the use of these grafts is thought to be ideal in the treatment of atrophic rhinitis.

Declarations

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Allografts Use in Nasal Reconstruction

16

Pier Giorgio Giacomini, Valentina Rosati, Eleonora Ciaschi, Andrea Gravina, and Stefano Di Girolamo

16.1 Introduction

The outcomes of destructive processes of the nasal structure such as infection, chronic inflammation, or resective procedures can lead to the need of complex reconstruction of the nasal framework [1]. Various types of grafts and implants have been employed [2]. When dealing with a nasal reconstruction of whatever kind, the surgeon is faced by a clinical dilemma: which is the best material for reconstructive purposes in that patient? The materials used for augmentation are therefore an important issue among reconstructive rhinoplasty surgeons [3, 4]. A basic differentiation must be outlined between the terms of grafts and implants: a graft is made of tissue either from the same patient (autograft) or from a member of the same species (homograft). Implants are synthetic and if implantable are called alloplasts [5]. Alloplastic material is deemed desirable if noncarcinogenic, nonallergenic, readily available, resistant to mechanical strain, and entirely reabsorbable and still reliable. It is commonly perceived that autologous grafts are the first choice for augmenting the nose; unfortunately, this material is not always available or sufficient in cases of atrophic changes of the nose of whatever cause to fulfill the needs. However, limited availability, unpredictable resorption rates, difficulty of handling, and donor-site morbidity are possible drawbacks. In such instances, other choices must be considered, and alloplastic materials can represent an attractive alternative tool to take into account [6]. On the other hand, their efficacy complications and limited usage are

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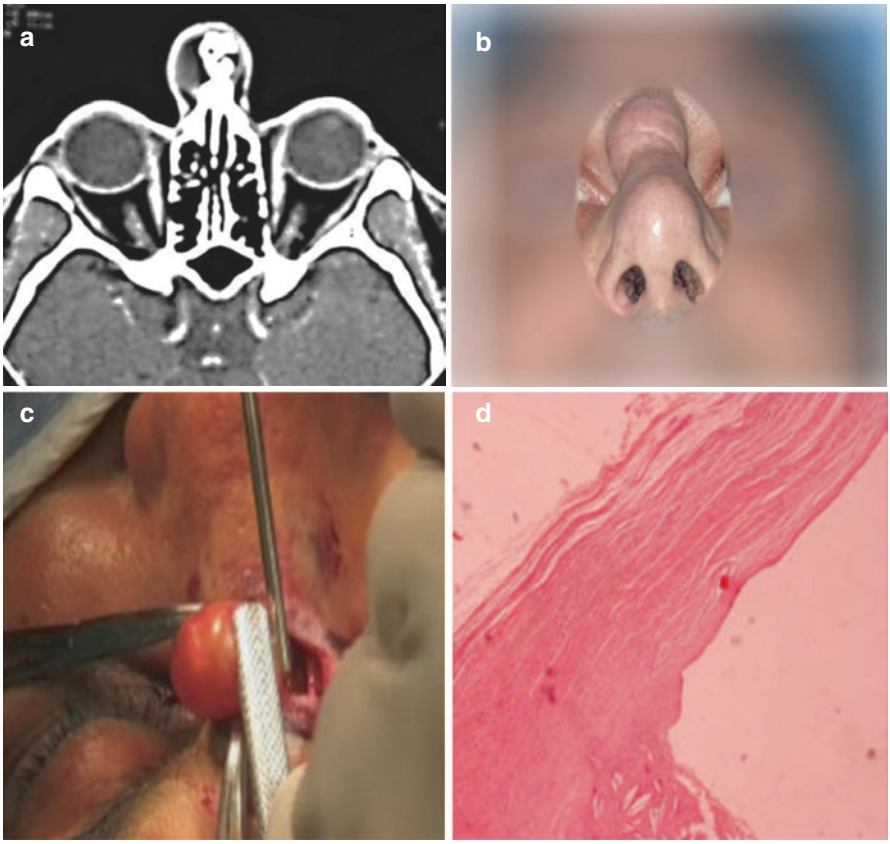

Fig. 16.1 (**a**) CT scan and pathology specimen showing foreign body cystic reaction. Fibrous capsule with implant inside. (**b**) Latex implant of the dorsum (implanted 10 years previously), at moment inflamed, cistic and mobile, removed. (**c**) The removing of latex implant. (**d**) A fibrous capsule with implant inside

debated, such not uniform feelings and disputed possibilities have given rise to the development of different technologies to possibly reach ideal grafting substance (Fig. 16.1). In Western countries, surgeons prefer costal or auricular cartilage when septal cartilage is not available or insufficient, whereas alloplastic materials are more widely used in Asia [7]. Since the very beginning of the rhinoplasty history, many efforts have been made over time to use implants such as gold, iron, ivory, paraffin, celluloid, glass, and cork, eventually discorded due to unsurpassable troubles [8] (Figs. 16.2 and 16.3). Today, commonly used alloplastic materials are silicon, Gore-Tex® (Surgiform Technology, SC, USA), Medpor® (Stryker Corporate,

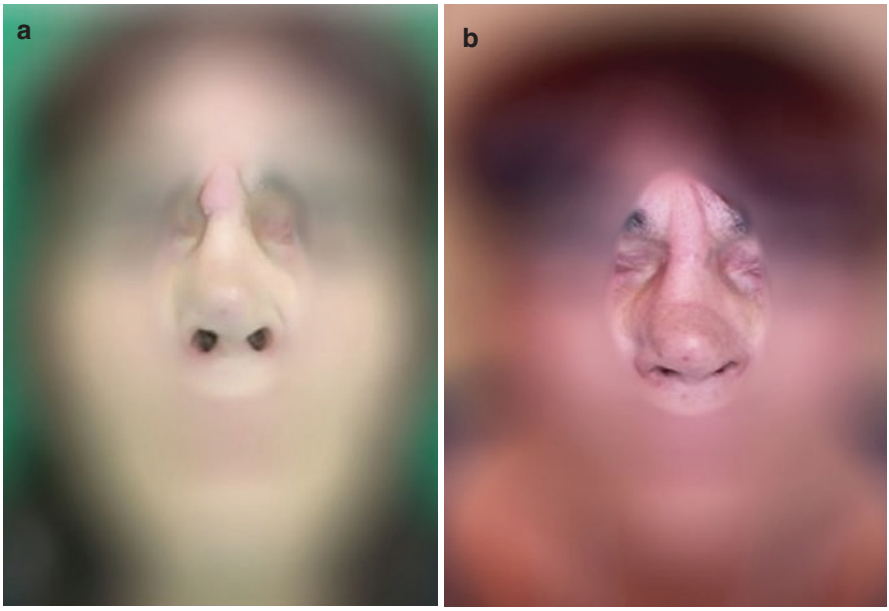

Fig. 16.2 (**a**) Kirschner steel wire and preserved costal cartilage implant of dorsum (10 years previously), for cocaine abuse outcomes. (**b**) Picture 6 months after removal

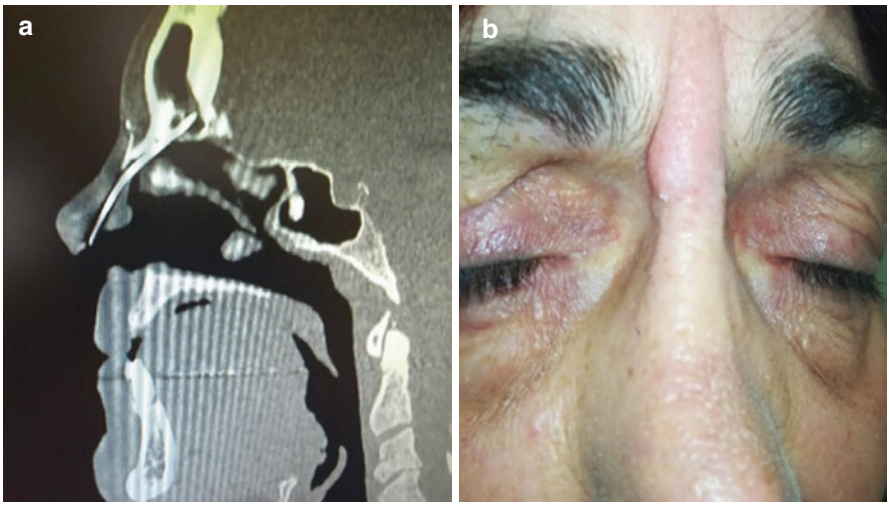

Fig. 16.3 (**a**) CT scan, showing implant and the infected. (**b**) Mobile dorsal implant

MI, USA), and polydioxanone plate (PDS Flexible Plate, Johnson & Johnson Company, Langhorne, Pennsylvania, USA) [9]. An overview of their pros and cons will be conducted on the basis of the literature data and personal experience to highlight their possible use in case of atrophic nose outcomes that require surgical correction.

Some exemplificative clinical cases of patients treated at the ENT Dept., School of Medicine, University of Rome Tor Vergata, at Nose Plastic Surgery Clinic in the past 10 years for complications associated with alloplastic materials used in atrophic rhinitis of various etiologies are reported. Clinical profiles: eight cocaine abuse, one purulent chronic infection, two outcomes of facial trauma, and one previous nasal surgery. M/F ratio: 1:4. The patients' age ranged from 42 to 81 years (mean: 49 years). The follow-up period was 3–15 years (mean: 4.2 years). All had been treated elsewhere for augmentation rhinoplasty with alloplastic materials end eventually revised for complications occurred. Type of alloplastic materials used, complications developed, and results obtained were revised by medical charts, photo documentation, and histopathologic data examined. Literature data were considered in order to define alloplastic materials possibilities in this kind of nasal reconstruction.

16.2 Type of Allografts

Different alloplastic materials are used today for nasal tissue augmentation with differences related to the ethnic differences, availability of material, costs, and surgeon's experience and preference.

16.2.1 Silastic

Solid silicone rubber, or Silastic (Silastic sheeting, Dow Corning, Midland, Michigan, USA), is nonporous, exhibits no vascular or tissue ingrowth, and elicits minimal inflammatory response. It can be easily sculpted to the desired shape. However, Silastic has been shown to exhibit micromotion, leading to the formation of a thick fibrous capsule [9]. Augmentation rhinoplasty by silicone implants is widespread in Asian countries but is almost abandoned in Caucasians [7].

This is a highly biocompatible, nontoxic, nonimmunogenic, easily formable, chemically stable, and inexpensive material. Asians thick nasal skin may be involved in the decrease of implant extrusion and benefits of silicon allografts are widely reported [10–13]. Infection, capsular contracture, extrusion, implant shift, and calcification that may occur up to over 35% following its use all over the body are also reported [14–18].

In the personal experience based on five cases (Fig. 16.4) of silicone nasal dorsal implants removal (two Asian, three Caucasians, MF ratio 1:4, age range 38–62 years)

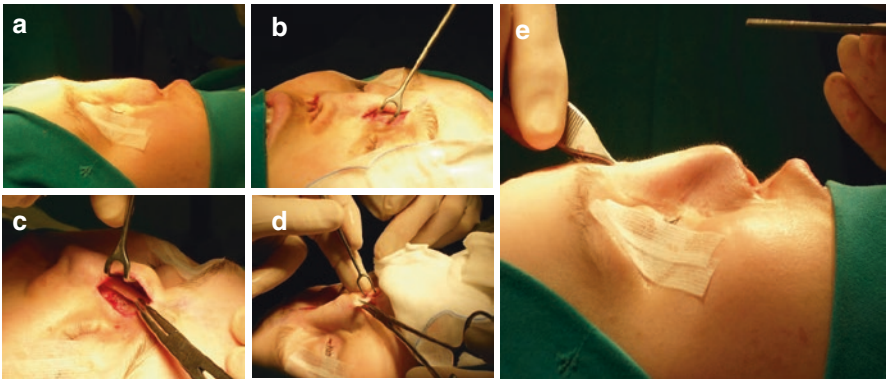

Fig. 16.4 Silicone nasal dorsal implants removal and olecranon bone autografting, cocaine outcomes: (**a**) a preoperative view. (**b**) Silicone implant removal. (**c**, **d**) Intraoperative views. (**e**) Final result

infection and capsule are the main drawbacks for the late complications leading to extrusion and shift of the implant (Fig. 16.5).

It must be noted though that individual differences are obviously present and surely affect the rate of complications. Silicone implants have shown the highest overall complication rate (13%) among alloplastic materials. It has been noted that complications decrease if silicone is covered with autologous tissue (8%), which may lower the damage that occurs over time [7].

16.2.2 Gore-Tex®

Gore-Tex® was introduced in nasal surgery in the late 1980s of the last century [19] (Rothstein and Jacob, 1989) claiming biocompatibility, an allergenicity, tissue integration, and structural stability. These characteristics derive from the porous texture of Gore-Tex® (10–30 μm size pores) that allows fibroblasts to grow into the pores, reducing the inflammatory response and capsular contracture. In the personal experience based on four cases of Gore-Tex, nasal implants removal (all Caucasians, MF ratio 1:2, age range 42–71 years) infection and capsule are the main drawbacks for the late complications leading to extrusion of the implant (Fig. 16.6). Nevertheless, Godin et al. [20], Conrad and Gillman [5], and Jin HR et al. [21] found a 2.5–3.7% complication rates. Jang et al. [22] and Hiun-Soo K. et al. [3] in 2014 examined the foreign body reaction, focal tissue ingrowth, calcification, decomposition, and thickness changes with Gore-Tex®, with similar results. It is felt that weakness against physical shock, uncertain ingrowth of the fibrovascular tissue into the tissue, difficulty in removal, and volume reduction are contraindications to the use of this material [23]. Literature studies suggest that Gore-Tex® and silicone implant may present similar failure rates. Nevertheless, specific analysis of the dorsal augmentation of Asian patients recently showed that silicone and Gore-Tex have an important

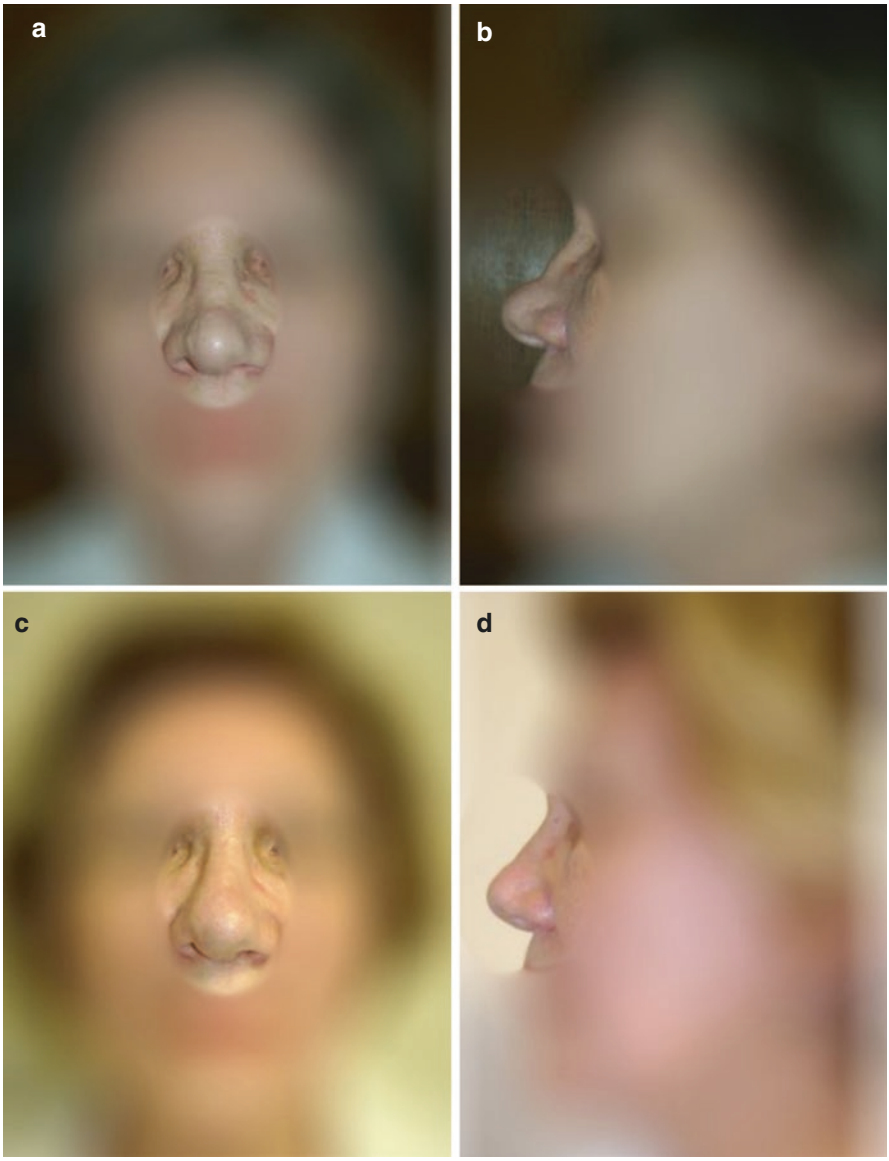

Fig. 16.5 (**a**, **b**) Postinfective (nasal osteomyelitis in childhood) nasal atrophy. Previous nasal reconstruction with silicon dorsal implant eventually infected and removed. (**c**, **d**) Reconstruction with conchal cartilage autografts

role due to their ease of use and low donor-site complications when employing specific technical tips in their use [24]. In Asians, Gore-Tex implants were effective and safe for use in primary and revision rhinoplasty, thus Gore-Tex can be considered as an alternative material for dorsal augmentation rhinoplasty but turned out not to have definite advantages over the silicone implants [25].

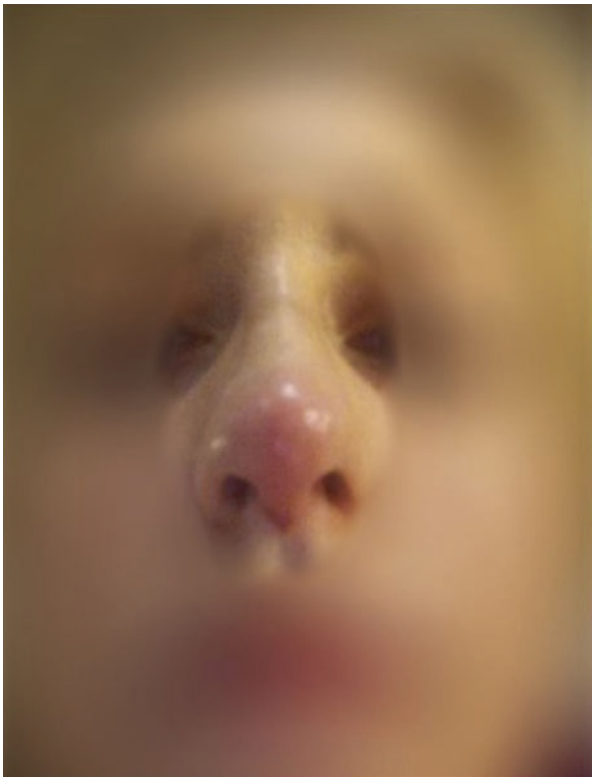

Fig. 16.6 Gore-Tex implant of the tip (3 years previously), recently infected and eventually substituted with conchal autograft

16.2.3 Medpor®

Medpor® has a broad range of applications and porous high-density polyethylene pHDPE (Medpor®) claims biocompatibility and ingrowth of connective tissue. It is used from the 1980s [26] but extrusion and infection are reported by its use in different fashion according to the kind of graft it is used for in nasal surgery. pHDPE is reported to be safer as a spreader graft than as a columellar strut [27–31]. pHDPE as a columellar strut has 21.24%, infections, five times higher than 4.11% as the dorsal onlay. Skouras et al. [32], Gentile et al. [33], and Scopelliti et al. [34] reported success using Medpor as dorsum implants and columella struts in 55 out of 58 patients. Yaremchuk et al. [35] offered the following three pearls for successful application of Medpor in open rhinoplasty: sufficient subperiosteal exposure of augmented region, solid fixation of the implant to the bone beneath, and in-place contour the implant.

In closed rhinoplasty, dissection of an appropriately sized pocket and carving a rough surface on the implant are crucial. It must be noted though that in case of need, surgical removal of Medpor® is extremely complicated. In the personal experience based on three cases of Gore-Tex, nasal dorsal implants removal (two Asians and one Caucasian, all females, age range 36–58 years) infection was the main drawback for the late complications leading to extrusion of the implant

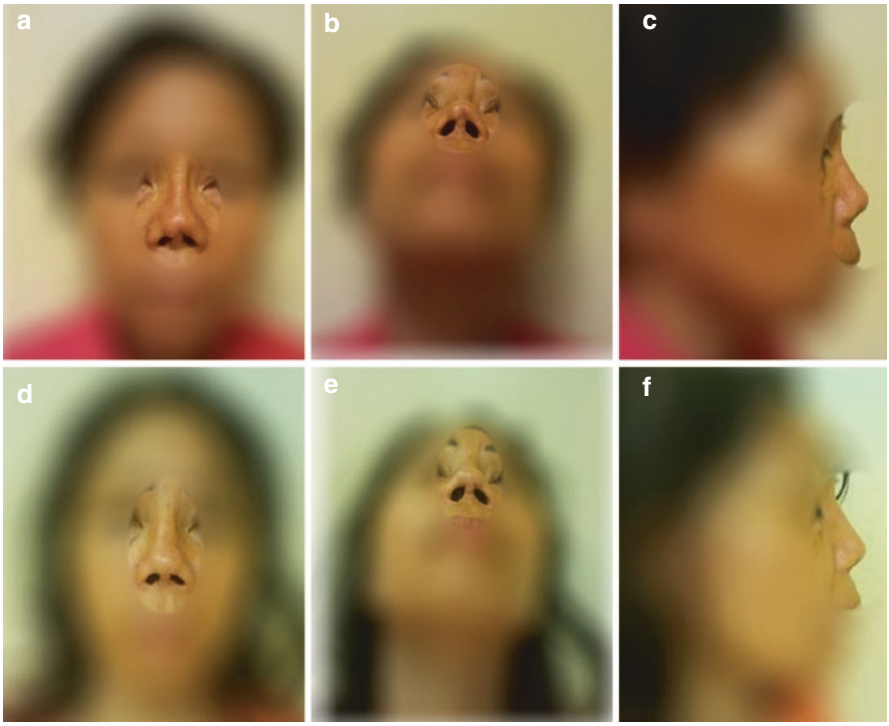

Fig. 16.7 (**a**, **b**, **c**) Medpor implant of the dorsum (7 years previously), infected and partially extruded; (**d**, **e**, **f**) 3 months after substitution with conchal autograft

with markedly difficult removal due to tight adherence to the surrounding tissues and atrophy of the overlying skin (Fig. 16.7). This material adheres very sturdily to mucosa and perichondrium, indicating a thriving surrounding tissue and vascular ingrowth [3]. In case of need, it is very difficult to remove Medpor without causing dramatic scarring and laceration of the overlying nasal envelope [36, 37]. Medpor may be satisfactory on the aesthetic and functional point of view but its validity is jeopardized by the potential damage to receiving area tissue (Fig. 16.8).

16.2.4 PDS®

PDS® is a colorless crystalline resorbable polymer (polydioxanone) that is degraded by hydrolysis and completely metabolized in the body with no interference with healing. It has been experimented for septal reconstruction with positive effects on healing and cartilage regeneration and eventual complete resorption of the graft itself [38]. PDS plates have been used in rhinoplasty, although quality long-term studies are lacking [9].

Fig. 16.8 Medpor implant removed

16.3 Conclusion

In an effort to compare the results of alloplast implants versus autografts, Liang X. et al. [7] carried out a meta-analysis of autologous costal cartilage (ACC) versus alloplastic implants use in rhinoplasty. They found a higher overall complication rate (14%) for ACC compared with that of other implants. It must be noted that ACC was broadly used in revision rhinoplasty compared to other materials; ACC is preferred in revision rhinoplasty, which may explain its association with higher complication rates. Gore-Tex was associated with the lowest overall complication rate (6%). ACC, Medpor, and Gore-Tex achieved outcome rates of 93% or greater in both functional and aesthetic domains. Noteworthy, alloplastic materials always have the risk of infection, extrusion, or displacement. They conclude that safety discrepancy between alloplastic material and ACC may narrow down or even reverse in the long run.

Different possible complications to consider when using implants and grafts:

1. Movement and contour irregularities of implants are untoward outcomes to be considered since the long-term ability to camouflage soft-tissue deficits is important. Several studies report the susceptibility for movement and contour irregularities of various implanted materials; in a review on these, Ferril et al. [9] concluded that "the propensity for movement, extrusion, and infection precludes the use of pHDPE and silicone rubber in the vast majority of rhinoplasty cases".

The placement of a rigid synthetic material in an inherently mobile structure likely leads to the high rate of complications.
2. Infection is another potential complication of implants: in a series analysis Winkler et al. [39] identify use of alloplast as significant risk factors for postoperative infection, pHDPE as a columellar strut, prior septoplasty or rhinoplasty, diabetes mellitus, and ePTFE as a dorsal onlay graft. Removal of infected allografts is usually mandatory, immediate or delayed reconstruction is still under debate, extrusion may follow infection or movement of the graft.
3. Reabsorption may also occur using reabsorbable alloimplants such as PDS [40].

In conclusion, it can be noted that alloplastic implants in rhinoplastic surgery have acceptable complication rates and can be used when autogenous materials are unavailable or insufficient. Outcomes with Medpor or Gore-Tex implants may be slightly better than those with silicone [41]. Based on the personal experience and literature data, it seems that alloplastic grafts in nasal reconstruction of atrophic noses are still a second choice, especially in Caucasian patients, since their ease of use is counteracted by a high complication rate. Considering what and how to support in the nasal structure and what technique to use, it is of utmost importance to know the mechanism involved in alloplastic material interaction and wound healing. This is a priority to prevent alloplastic-related complications and to find the most suitable alloplastic material according to each case. These characteristics have to be taken into account to precisely tailor their use for clearly selected cases. Many alloplastic materials have been introduced and discarded because of their serious complications, testifying so that the ideal graft is still unavailable [42]. Due to such a situation, nasal augmentation in atrophic rhinitis sequelae can be performed by alloplastic materials if age, ethnicity, and area to reconstruct are compatible with a low incidence of complications expected. The ideal candidates may be in our view preferably Asian, older age, or with major general health-related problems, with no need of major reconstruction of the lower third of the nose. No ideal or all-time-good implant is available at moment and differences among grafts must be considered. However, each patient has unique characteristics, a shared decision-making process is deemed with the patient to discuss risks and benefits of each choice and guide expectations. Pursuit for an ideal nasal implant still continues. Considering what and how to support in the nasal structure and what technique to use, is of utmost importance to find the most suitable alloplastic material according to each case.

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